Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

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Stakeholder	Document	Page No	Line No	Comments	Developer's response
British Nuclear Medicine Society	Evidence Review A	008	004 - 005	We acknowledge committee's balanced decision and preference for categorising thyroid scintigraphy as 'not routinely performed' instead of 'not indicated' etc. However, the statement reads rather vaguely and does not reflect the recommendation outlined in the newest Society of Nuclear Medicine and European Society of Nuclear Medicine practice guideline (Avram *et al*., JNM 2022). We agree on the fact that the current practice of radioisotope scans is largely variable. However, we would favour a more specific comment on the topic, e.g. 'Radioisotope scans are used for the initial diagnosis of thyroid cancer, depending on clinical factors/stratified based on, for example, tumour size, tumour phenotype/histological grade, tumour invasiveness, patient's age and risk factors.' To note, according to the new international guidelines on thyroid cancer, neck ultrasound, serum thyroid-stimulating hormone, as well as thyroid scintigraphy are recommended to select high-risk nodules for fine-needle aspiration and filter out low-risk nodules from inappropriate additional procedures. Depending on the tumour phenotype detected on the initial cytology and stratified, FNA can be complemented by assessment of specific radioisotope	Thank you for your comment. We are pleased that you agree with the recommendation, and we acknowledge that you would prefer further details about when they should be used. However, the word 'routinely' was used to indicated that radioisotope scans might be useful in rare and specific circumstances for the initial diagnosis of thyroid cancer. The committee decided not to provide examples as they would be extremely context dependent and would not demonstrate the complexity of decision making. The committee do not agree that radioisotope scans should be used for the initial diagnosis of thyroid cancer, and we do not see any evidence in the cited Society of Nuclear Medicine and European Society of Nuclear Medicine practice guideline to support this practice. Therefore, the committee believe the recommendation to not routinely use radioisotope scans for the initial diagnosis of thyroid cancer is the right recommendation which also reflects current practice.

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

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				imaging with Tc99m-MIBI (SESTAMIBI) or F18-FDG PET or F18-DOPA PET (Giovanella *et al*, EJNMMI 2019).	
British Nuclear Medicine Society	Evidence Review A	012	002 – 003, 006 - 008	RAI is indeed given for patients after thyroidectomy for **differentiated thyroid cancer**. Thus, for the vast majority but not for all of thyroid cancers, tumour phenotype being the important determinant. The 2 statements on RAI are very similar and might be combined or, at least, set one after each other. Suggestion: '**RAI is recommended in people who have had a total or completion thyroidectomy** (irrespective to the criteria highlighted in 1.3.3.) *and depending on tumour phenotype (!)*.'	Thank you for your comment. The treatment recommendations only relate to differentiated thyroid cancer. We have made this clearer in our sections headings in the guideline and therefore have not mentioned tumour phenotype in the recommendations. The recommendations are separate because one is a strong 'offer' recommendation while the other is a 'consider' recommendation. The order has been carefully selected to highlight firstly those people that should have RAI ablation, then those that shouldn't and finally the people remaining that could be considered for RAI but the evidence does not support a stronger recommendation of offering or not offering.
British Nuclear Medicine Society	Guideline	003	008 - 009	There is an increasing number of thyroid nodules/abnormalities detected on standard imaging performed for another indication. For example, a patient with a suspected incidental thyroid cancer seen on FDG PET-CT done for another cancer diagnosis or follow-up. This is a fairly common occurrence and could be addressed.	Thank you for your comment. The committee think that the first bullet point captures this. They have avoided stating how lumps, nodules or swellings have been identified and kept the point generic to all lumps.

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

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				Suggestion: 'Explain to people with suspected thyroid cancer: • That not all lumps, nodules or swellings in the thyroid are cancer • **That not all incidental findings in the thyroid described on conventional imaging represent cancer (…)**	
British Nuclear Medicine Society	Guideline	012	002 - 008	Indeed, RAI is given for patients after complete thyroidectomy for differentiated thyroid cancer. However, RAI is fully recommended also to ablate residual disease after thyroidectomy, as adjuvant disease, and also as potentially curative treatment of proven metastatic or recurrent disease. This should be considered in the draft scope.	Thank you for your comment. We included a stratification of the evidence in the review (evidence review I) so that we would distinguish between evidence related to ablation (removing any remnants of thyroid tissue) and treatment (treating any remaining thyroid malignancy such as residual lymphatic disease or metastatic disease). However, we only identified evidence related to ablation. We have made the recommendations clearer to note that they only apply to the initial ablation. The committee agree that RAI has a part to play for recurrent disease but we did not includes this as a review in the guideline and therefore the committee have not made recommendations in this area.
British Nuclear Medicine Society	Guideline	012	004 - 005	Indeed, RAI is not recommended in T1a thyroid cancers. Additional comment on RAI in other low-risk thyroid cancers (i.e. pT1b-T2) should be added to the scope draft.	Thank you for your comment. The guideline has been updated to include new trial evidence (ESTIMABL 2 trial - Leboulleux S et al. Thyroidectomy without radioiodine in patients in low-risk thyroid cancer. NEJM 2022; 386:923-32). Evidence report J has been updated with the new evidence and the committee's

Thyroid cancer: assessment and management

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23/06/2022 to 04/08/2022

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				According to current guidelines, RAI for other low-risk differentiated thyroid cancer patients (**pT1b-T2**) remains controversial but not contraindicated. Despite various iterations of the ATA guidelines advising against RAI in these patients, the newest European Association of Nuclear Medicine guidelines suggest that RAI could be taken in consideration (Tuttle *et al*, Thyroid 2019; Verburg *et al*., EJNMMI 2016).	interpretation of the evidence is contained in the committee discussion section. Based on this evidence the committee updated the recommendation to 'Do not offer RAI to people with T1a or T1b tumours including those with multifocal disease, unless there are adverse features or evidence of metastatic disease.' There wasn't evidence to recommend not offering RAI to those with T2 disease. As this would be a change in practice the committee recommend that RAI is considered in this group. The research recommendation has been narrowed to only cover T2 disease. The research protocol is available in appendix J of evidence report J.
British Nuclear Medicine Society	Guideline	012	010 - 017	With regard to RAI activity, there are a few additional points to be considered and potentially incorporated into the scope draft: -RAI is usually given based on patient's risk stratification; -additional radioisotope imaging should be part of therapy planning; -choice of RAI therapy dose. Who should get RAI needs to be risk stratified by iodine avidity, initial size of tumour, histological grade, patient age and gender and subsequent treatment by dynamic risk stratification.	Thank you for your comment. The guideline did not include reviews for risk stratification or radioisotope imaging before RAI and therefore no recommendations have been made in this area. The committee noted that radioisotope scans were used in the past but current practice has moved away from this. The committee agreed that in most cases RAI would be given at the lowest possible activity to fit in with the ALARP principle of keeping doses 'as low as reasonably practical' as stated IRME regulations on

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

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				This is done primarily by the use of radionuclide scans (iodine thyroid scintigraphy) and less by other imaging (e.g. US). Please note that demonstration of iodine avidity and cancer spread using radioisotope scans (iodine thyroid scintigraphy) represents the quintessential principle of radiothera(g)nostic approach that should guide personalised/individualised management. This is crucial in order to maximise benefit: reduce risk for each patient who belongs to a risk category and improve patient's outcomes after RAI. Therefore, integrating functional imaging information obtained with postoperative radionuclide scans (preablation radioiodine -I123, I131 or I124- scans) in the management algorithm is recommended	(https://www.legislation.gov.uk/uksi/2017/1322/contents/made). Therefore, they recommend higher activities only for high-risk groups, and a lower activity for all other people. This is in line with the evidence which suggested that higher activity RAI only provides a small benefit to a small number of people.
British Nuclear Medicine Society	Guideline	012	010 -017	The mentioned RAI activities are reflecting the current practice. However, it is felt that the wording is largely restrictive and does not allow the implementation of the newly proposed therapeutic strategies. The decision for RAI and the prescribed RAI activity depends largely on the goal of RAI as determined by estimated risk of persistent/recurrent disease. Please note that the 2022 SNM/EANM guidelines listed a number of suggested RAI activities in the context of therapeutic intent: -1.1 GBq and 3.7 GBq, as already mentioned,	Thank you for your comment. The committee recommends thyrotropin alfa for all people who are being offered radioactive iodine. The recommended activities for RAI fit the licenced activities for thyrotropin alfa from the summary of product characteristics (SPC). This states that is indicated for pre-therapeutic stimulation in combination with a range of 30 mCi (1.1 GBq) to 100 mCi (3.7 GBq). While the committee agree that there may be cases where a higher activity than 3.7GBq is warranted they noted that this would be in few cases, and would not be the initial activity chosen. The committee updated the

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

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				but also alternative activities of -5.6-7.4 GBq for treatment of advanced locoregional disease and/or small volume distant metastatic disease ->=7.4 GBq (maximum tolerable safe RAI dose) for treatment of diffuse distant metastatic disease. Moreover, dosimetry-guided activities/individualisation of RAI should be taken in consideration as a feasible and increasingly veto-ed option. (Avram *et al*, JNM 2022) Thus, although fixed activities of RAI are largely favoured in current practice for practical reasons, the NICE recommendation should not be restrictive on implementing the newest 2022 recommendations on RAI.	recommendation to note that these activities relate to the initial ablation. We did not include a review on dosimetry-guided activities/individualisation of RAI and therefore have not made a recommendation or statement on this in the guideline.
British Nuclear Medicine Society	Guideline	021	012	It should read 'F18-FDG PET' instead of 'PET'.	Thank you for your comment. We have updated this to F-18 FDG PET-CT in the guideline and evidence report.
British Thyroid Foundation	Guideline	004	001	Insert 'lifelong' before 'thyroid hormone replacement' for consistency with the third point in recommendation 1.1.9	Thank you for your comment. The committee agree and have added 'lifelong' before 'thyroid hormone replacement'
British Thyroid Foundation	Guideline	004	018	Please consider giving further details about who the key worker is. We have never heard patients or clinicians referring to a patient's 'key worker'. Is it the doctor, surgeon, nurse specialist or other? This may	Thank you for your comment. The committee are quite surprised by your comment. 'Key worker' is an accepted term and all people with cancer in England and Wales are assigned one. They agreed it will

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

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				vary between different hospitals and departments of course but we think 'key worker' is too vague and unfamiliar a term. It should also state here an requirement how this person can be contacted (see comment 4 below).	usually be a clinical nurse specialist but this isn't always the case. The term 'key worker' is also used in other NICE cancer guidelines. The point about who to contact has been merged with the key worker point so that the bullet point now states 'who their key worker is and who to contact for more information'. A little more detail on who the key worker is has been added to the committee discussion (Section 1.1.8.2 in Evidence Review R).
British Thyroid Foundation	Guideline	004	023	Include breastfeeding	Thank you for your comment. The committee agree and 'breastfeeding has been added to the recommendation.
British Thyroid Foundation	Guideline	004	028	Could this comment be combined with the first bullet point in this section (see comment 2 above)?	Thank you for your comment. The committee agree and have merged these two bullet points to state 'who their key worker is and who to contact for more information'.
British Thyroid Foundation	Guideline	005	007	Delete 'and' if you include the suggested addition below.	Thank you for your comment. The committee agree and have deleted 'and' and added the suggested wording 'and how to contact them' to the recommendation. The bullet point now states 'when to seek advice from a healthcare professional, who that healthcare professional should be.and how to contact them'.
British Thyroid Foundation	Guideline	005	008	Insert ',and how to contact them.' We believe this is essential to include in the guideline as unfortunately many patients still report to us that they have not been given this information or that they cannot easily contact the relevant person.	Thank you for your comment. The committee agree and have added this to the recommendation. The bullet point now states 'when to seek advice from a healthcare professional, who that healthcare professional should be.and how to contact them'.

Thyroid cancer: assessment and management

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British Thyroid Foundation	Guideline	006	016	'Active' does not need to be capitalised. If it does it should be consistent throughout the document.	Thank you for your comment. This has been corrected.
British Thyroid Foundation	Guideline	010	004	'Active' does not need to be capitalised. If it does it should be consistent throughout the document.	Thank you for your comment. This has been corrected.
British Thyroid Foundation	Guideline	014	013	It may be helpful to include a reminder that patients who have had TSH suppression for many years may be very reluctant to have a reduction in the L-T4 as they had been advised at diagnosis that they would need suppression for life. The lower dose (however small the change) may leave them feeling unwell. It is important that the clinician/ nurse specialist makes time to discuss the reason for the change in treatment. The dose reduction should be managed carefully and the patient given time and support to get used the change.	Thank you for your comment. The committee agree and think this is a good idea. The recommendation has been updated to state: Offer a review to people who have had ongoing TSH suppression for more than 10 years. Decide whether the TSH suppression can be reduced after an individualised assessment of risks and benefits, and explain that: • lifelong suppression is not necessary unless they have high-risk or metastatic disease • **avoiding complete TSH suppression may reduce the risk of developing bone and cardiac problems**
British Thyroid Foundation	Guideline	General	General	Information for the Pubic We note that the Guideline recommends that patients should be given verbal and written information to help them understand their diagnosis and treatment options. In the NICE guideline NG145 there is a section entitled 'Information for the public' which include links to reputable sources of further information ('Where can I find out more?). It would be very helpful if this guideline includes a similar section with links to	Thank you for your comment. Similar to NG145 there is a section on 'Information for the public' added with the published guideline. This will link to relevant organisations.

Thyroid cancer: assessment and management

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23/06/2022 to 04/08/2022

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				the patient organisations which provide accessible and reliable information in this field.	
Butterfly Thyroid Cancer Trust	Guideline	009	013 - 015	1.3.2 Currently there is an ongoing clinical trial [HOT Hemi or Total looking into this issue and this should be acknowledged.	Thank you for your comment. This is acknowledged in the committee discussion of evidence report H. We will make the NICE surveillance team aware of the study.
Butterfly Thyroid Cancer Trust	Guideline	010	001 - 003	Patients should be made aware of and offered inclusion into the HOT trail where appropriate and available ,this will produce much needed research into this area for low risk thyroid cancer .	Thank you for your comment. Recommending people for inclusion in the HOT trial is beyond the scope of this guideline. The trial web page (https://www.isrctn.com/ISRCTN17004671) lists the participating centres. It is anticipated that anyone attending these centres may be considered for inclusion in the HOT Trial if they meet the inclusion criteria.
Butterfly Thyroid Cancer Trust	Guideline	011	009 - 035	The recommendation for use of thyrotropin alpha should be made stronger from 'consider' to 'offer'. This has been used widely across the UK for twenty years and not recommending it is a massive back ward step and would place the UK out of step globally in the treatment of thyroid cancer. We know that patients who have to undergo withdrawal from thyroxine will stay in hospital longer [increasing cost to the hospital] and more importantly for the patient they are unwell and unable to return to work or normal life for at least 6 weeks .Also these patients need to take liothyronine for two weeks before having treatment which is an added extra cost .Many	Thank you for your comment. After a further discussion with the committee and to avoid a potentially harmful disruption of current practice, the guideline has been changed to recommend that all people who are having radioactive iodine (RAI) should also receive pretherapeutic stimulation with thyrotropin alfa (recommendation 1.3.12). Differences in hospital length of stay were included in the health economic model as they directly affect NHS spending. Although only ESTIMBAL reported this outcome explicitly (0.2) an extrapolation based on HiLo (UK) found a similar number (0.1). The higher value from ESTIMABL was ultimately used in the

Thyroid cancer: assessment and management

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23/06/2022 to 04/08/2022

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				patients are young adults with young families to care for .	model as it could be directly taken from the study and did not require approximation or extrapolation (unlike HiLo). Likewise, the impact of liothyronine was also assessed in many scenarios of the analysis and its price trend in England extensively discussed. Time off work and equality considerations could not be incorporated into the economic model but were widely discussed by the committee. They are reported in the rationale and committee discussion of the guideline and are part of the reason the committee changed the recommendation to a stronger 'offer' recommendation.
NCRI-ACP-RCP	General	General	General	The NCRI-ACP-RCP is grateful for the opportunity to respond to the above consultation. In doing so we would like to endorse the responses submitted by the BNMS and RCR. We would also like to comment as follows.	Thank you for your submission. We have responded to each comment in turn.
NCRI-ACP-RCP	Guideline	011	009 - 012	**Rec 1.3.12 – Consider thyrotropin alfa for pretherapeutic stimulation for any people with thyroid cancer who can have THW (including those with distant metastases; see recommendation 1.3.14) who are having RAI ablation or treatment.** Our experts would prefer that Thyrogen should be 'offered' rather than 'considered', in view of the	Thank you for your comment. After a further discussion with the committee and to avoid a potentially harmful disruption of current practice, the guideline has been changed to recommend that all people who are having radioactive iodine (RAI) should also receive pretherapeutic stimulation with thyrotropin alfa (recommendation 1.3.12).

Thyroid cancer: assessment and management

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				significant patient benefits that Thyrogen provides over THW	
NCRI-ACP-RCP	Guideline	012	011 - 012	**Rec 1.3.18 – Consider RAI with an activity of 3.7 GBq for high-risk groups, such as people with T4, N1b or M1 disease or aggressive subtypes, or for whom multiple ablations should be avoided. This includes people with significant comorbidities such as cardiovascular disease, mobility issues or complex social concerns.** Our experts question whether patients with M1 disease should be included in this recommendation. These patients would usually be treated with an activity higher than 3.7GBq	Thank you for your comment. The committee recommends thyrotropin alfa for all people who are being offered radioactive iodine. The recommended activities for RAI fit the licenced activities for thyrotropin alfa from the summary of product characteristics (SPC). This states that is indicated for pre-therapeutic stimulation in combination with a range of 30 mCi (1.1 GBq) to 100 mCi (3.7 GBq). While the committee agrees that there may be cases where a higher activity is warranted they noted that this would be in few cases, and would not be the initial activity chosen. The committee updated the recommendation to note that these activities relate to the initial ablation.
NCRI-ACP-RCP	Guideline	013	017 -018	**Rec 1.4.2 – Offer thyroid hormone at doses that will suppress TSH to below 15 0.1 mIU/litre, to people who have had total or completion thyroidectomy and RAI. TSH suppression should be continued for at least 1 year after initial treatment has been completed.** Our experts note that this states that TSH suppression should be continued for at least 1 year after initial treatment, this is not consistent with the next recommendation (1.4.3) which recommends dynamic	Thank you for your comment. The committee agree and have amended the recommendation to state '…TSH suppression should be continued until follow up review at 9 to 12 months after initial treatment has been completed.'. This makes it consistent with the following recommendation 1.4.3 which recommends using dynamic risk stratification to determine further management. This includes advising when TSH suppression can be reduced.

Thyroid cancer: assessment and management

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23/06/2022 to 04/08/2022

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				risk stratification (DRS) is carried out at 9-12 months. In many patients the TSH suppression can be relaxed after DRS. The recommendation could state 'the need for TSH suppression should be reviewed after dynamic risk stratification'	
NCRI-ACP-RCP	Guideline	016	007 - 011	**Rec 1.5.7 – Consider the following if using a stimulated thyroglobulin test:** • **less frequent follow up where appropriate and more relaxed TSH suppression if stimulated thyroglobulin is below 2 microgram/litre (low 8 risk)** • **continuing TSH suppression if stimulated thyroglobulin is between 2 microgram/litre and 10 microgram/litre (indeterminate risk).** • **further investigations and treatment if stimulated thyroglobulin is 10 microgram/litre or more and there is no resectable disease.** Our experts note that this is inconsistent with the BTA guidelines which recommend relaxing TSH suppression if the stimulated Tg is <1 (not 2), and that indeterminate risk is defined by a stimulated Tg of	Thank you for your comment. The committee agree and have updated the recommendation and rationale replacing 2 with 1 as you suggest. The committee discussion of evidence review P has also been updated to reflect this.

Thyroid cancer: assessment and management

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23/06/2022 to 04/08/2022

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				between 1 and 10 (not 2 and 10). See also page 44, lines 11-13	
NCRI-ACP-RCP	Guideline	031	012 - 013	**Other indications would include signs of metastases or a suspicious symptom such as a cough** Our experts question whether this sentence be moved further down the page to the section on more advanced disease (line 20 onwards)	Thank you for your comment. This point is to highlight the circumstances when cross sectional imaging may be warranted in T1 and T2 disease. The statement has been placed here because it relates to the first recommendation in the cross sectional imaging section. We have added a little more detail in the sentence to make this clearer. It now states 'Other indications that would suggest cross-sectional imaging may be useful, include signs of metastases or a suspicious symptom such as a cough.'
NCRI-ACP-RCP	Guideline	044	025	**Rec 1.5.8 Consider the following if using a highly sensitive assay that can detect 14 thyroglobulin levels lower than 0.2 microgram/litre** Our experts question whether this should this read ' 0.2mcg/L and 1mcg/L', not '0.2mcg/L and 0.1mcg/L'	Thank you for your comment. We think your comment relates to the text in the benefits and harms section on page 7 of the consultation version of evidence review P which covers this topic. We agree and have corrected the text accordingly which should also be on page 7 of the final report.
NCRI-ACP-RCP	Guideline	General	General	These recommendations are for differentiated thyroid cancer, but the studies rarely included patients with follicular thyroid cancer as the majority of the patients in the studies had low risk PTC. Therefore, it is hard to give recommendations for follow up of FTC and also poorly differentiated thyroid cancer.	Thank you for your comment. The committee agree that studies rarely included people with follicular thyroid cancer and noted that historically, defining histopathological sub-types was not reported. They took this into consideration when making recommendations and agreed that in the absence of

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

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Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Our experts question whether this should be mentioned somewhere in the follow up section.	evidence the same recommendations would still apply to all people with differentiated thyroid cancer.
NHS England	Guideline	005	011	The heading is 'blood test' and yet 1.2.1 is not about blood tests. I would suggest an extra heading 'Presentation'.	Thank you for your comment. The following changes have been made: - the section title has been changed to 'Assessment and diagnosis'. - the cross referral to the NICE guideline on suspected cancer has been moved to above the section on blood tests. - the recommendation under the blood tests subheading has been edited to read 'See recommendations on thyroid function tests in the NICE guideline on thyroid disease'.
NHS England	Guideline	005	012	The inclusion of the reference to 'investigating thyroid dysfunction' does not seem relevant to the cancer theme of this guideline.	Thank you for your comment. The reference to 'investigating thyroid dysfunction' is included because thyroid cancer usually presents as a lump in the neck. It won't be known at this stage whether the lump is malignant or not. The committee agreed that thyroid function blood tests are an important first step in the pathway for any thyroid dysfunction or enlargement. Therefore, they agreed it was important to join up the recommendations in the pathway with the NICE guideline Thyroid Disease

Thyroid cancer: assessment and management

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					(https://www.nice.org.uk/guidance/ng145). The recommendations have been updated and: - the cross referral to the NICE guideline on suspected cancer has been moved to above the section on blood tests. - the recommendation under the blood tests subheading has been edited to read 'See recommendations on thyroid function tests in the NICE guideline on thyroid disease'.
NHS England	Guideline	005	013	The reference takes you to one line in "recommendation on referral for suspected thyroid cancer" and as such it would be good to just include that recommendation again here under the heading 'presentation' and reference it.	Thank you for your comment. The NICE style is to link to the recommendation and not repeat it. This is to ensure that if a recommendation from another guideline is updated, then the advice will not be out of date.
NHS England	Guideline	General	General	The document does not mention primary care or general practice and the potential parts of the pathway that might be carried out in primary care or require follow up in primary care.	Thank you for your comment. The committee agreed diagnosis, treatment and follow up of thyroid cancer would be done in secondary care which makes it difficult to make the guideline applicable to primary care. NICE's guideline on thyroid disease (https://www.nice.org.uk/guidance/ng145) covers the earlier part of the pathway including recommendations related to investigating suspected thyroid dysfunction and thyroid enlargement, and treatment of non-malignant thyroid enlargement. The NICE guideline on suspected cancer (https://www.nice.org.uk/guidance/ng12) covers referral. Both those guidelines are cross referred to at the relevant points in the thyroid cancer guideline.

Thyroid cancer: assessment and management

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NHS Greater Glasgow & Clyde	Guideline	006	014 - 015	Rec 1.2.9 It is not felt to be particularly helpful to recommend that for those choosing to use EU-TIRADS that they use a different FNA threshold to that which the established system recommends. There are numerous grading systems with differing thresholds for FNA and this will very likely only add confusion in practice.	Thank you for your comment. Following stakeholder comments the committee agree that the recommendation referring to EU-TIRADS is unhelpful and have removed it from the guideline. The guideline no longer highlights any particular scoring system. There is still a cross reference to the NICE guideline on thyroid disease (https://www.nice.org.uk/guidance/ng145) which recommends 'When making decisions about whether to offer fine needle aspiration cytology, use an established system for grading ultrasound appearance'.
NHS Greater Glasgow & Clyde	Guideline	009	001 - 003	Rec 1.2.18 : "Consider cross-sectional imaging (CT of neck and chest, or MRI of neck and CT of chest) for people with T2 thyroid cancer if there are aggressive features on histopathology or their age or sex puts them at a higher risk" This is rather vague to add any clarity to an area where there seems to be quite a bit of variation in current practice. T stage is often only formally determined post-operatively. The main utility of cross-sectional imaging is for pre-operative surgical planning in locally advanced disease with extrathyroidal or retrosternal extension or in patients with lateral chain adenopathy. What combination of age and sex demographic is this recommending should have CT? We appreciate that this has been identified as a topic for further research Concern that CT is currently over-utilised in "staging" of differentiated thyroid cancer – there is rarely much	Thank you for your comment. The committee agree that this could be unhelpful and lead to an unwelcome increase in CT scanning without sufficient evidence. We have deleted recommendation 1.2.18 and added T2 disease to recommendation 1.2.17 which states. 'Do not routinely use cross-sectional imaging (CT or MRI) in people with T1 or T2 disease and no other indications'. The committee agreed that should there be other indications then cross sectional imaging would still be possible. The rationale associated with this recommendation and the benefits and harms section of the committee discussion in Evidence report G has been updated to reflect this.

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

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Stakeholder	Document	Page No	Line No	Comments	Developer's response
				to find beyond that seen on ultrasound which would alter the surgical plan. CT can be less sensitive than the iodine-131 ablation scintigraphy for distant metastases (and if contrast is given requires interim delay before radioactive iodine ablation) and often generates many anxiety-inducing incidental findings. This recommendation may lead to an unwelcome increase in CT without sufficient evidence base.	
NHS Greater Glasgow & Clyde	Guideline	017	004 - 007	Rec 1.6.2. Particularly regarding those with hemithyroidectomy only, there is currently insufficient evidence that ongoing ultrasound follow-up provides benefit in these typically low-risk patients. Ongoing ultrasound surveillance is more likely to yield false positive findings and has significant resource implications. Meanwhile ultrasound will in fact often fail to detect many of the inevitably present remnant papillary microcarcinomas which are often of no clinical/biological significance. The approach suggested by the European Society of Medical Oncology of a single post-operative ultrasound at 6-18 months in the hemithyroidectomy group would be more practical and pragmatic.	Thank you for your comment. The committee agreed there wasn't clear evidence on when and if ultrasound should be used after the initial follow up ultrasound. Therefore, they left it for the clinician to decide whether to do ultrasound at follow up reviews. We have added this to the rationale and updated the recommendation to state it is annual clinical follow up.
NHS Greater Glasgow & Clyde	Guideline	025 - 026	023 – 31, 001 - 006	"Ultrasound. Why the committee made the recommendations 1.2.5 to 1.2.10" There seems to be a lot of emphasis on EU-TIRADS here despite there being several other grading systems in use. How was it decided that EU-TIRADS was best in terms of simplicity of use? It is more of a pattern-based system. In such a system, like British Thyroid	Thank you for your comment. Following stakeholder comments the committee agree that the recommendation referring to EU-TIRADS is unhelpful and have removed it from the guideline. The original recommendation was made because the committee believed EU-TIRADS showed the most promising results. However, the committee agree that without

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

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Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Association and American Thyroid Association classification, nodules can be left difficult to classify, often falling under "indeterminate". This tends to be more difficult to use and learn to apply than a point-based TIRADS system. American College of Radiology TIRADS is a user-friendly, point-based system with comparable sensitivity and specificity to EU-TIRADS. It offers a size threshold for each grade of nodule for both FNA and follow-up so active surveillance of smaller sub-FNA nodules is built in.	evidence to recommend a whole system this gives too much emphasis to EU-TIRADS and may make it difficult to use or continue to use alternative systems such as BTA guidelines or ACR TIRADS. The guideline no longer highlights any particular scoring system. There is still a cross reference to the NICE guideline on thyroid disease (https://www.nice.org.uk/guidance/ng145) which recommends 'When making decisions about whether to offer fine needle aspiration cytology, use an established system for grading ultrasound appearance'. A review of the evidence on size for tumour was included as part of the guideline. As no evidence was found that met the protocol no recommendations made in this area. The protocol and details of this review are included as part of evidence report A.
NHS Greater Glasgow & Clyde	Guideline	026	012 - 013	"Ultrasound. Why the committee made the recommendations 1.2.5 to 1.2.10" EU TIRADS does not assess internal vascularity.	Thank you for your comment. Following stakeholder comments the committee agree that the recommendation referring to EU-TIRADS is unhelpful and have removed it from the guideline. The guideline no longer highlights any particular scoring system. There is still a cross refererence to the NICE guideline on thyroid disease (https://www.nice.org.uk/guidance/ng145) which recommends 'When making decisions about whether to offer fine needle aspiration cytology, use an

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					established system for grading ultrasound appearance'.
NHS Greater Glasgow & Clyde	Guideline	047	010 - 012	Context. Autopsy studies would suggest that there is no true increase in the prevalence of differentiated thyroid cancer over the last several decades. It is widely accepted that increased incidence is due to increased detection with more widespread use of high-resolution ultrasound and cross sectional imaging.	Thank you for your comment and support of the text in the context.
NHS Greater Glasgow and Clyde	Guideline	006	014	Rec 1.2.9 – We are concerned that this adapting the EU – TIRADS system will lead to an increased demand for FNAC which will have significant workload implications for radiology and pathology services. In addition to this, a significant number of patients with non-diagnostic FNAC (Thy1) will have unnecessary surgery. An alternative to EU – TIRADS would be ACR – TIRADS. The latter has been shown to outperform the former by reducing the number of unnecessary FNAs and surgery for benign nodules.	Thank you for your comment. Following stakeholder comments the committee agree that the recommendation referring to EU-TIRADS is unhelpful and have removed it from the guideline. The guideline no longer highlights any particular scoring system. There is still cross reference to the NICE guideline on thyroid disease (https://www.nice.org.uk/guidance/ng145) which recommends 'When making decisions about whether to offer fine needle aspiration cytology, use an established system for grading ultrasound appearance'.
NHS Greater Glasgow and Clyde	Guideline	017	004	Rec 1.6.2 – The recommendations suggest ultrasound at 6 -12 months for patients with T1(m) and then follow up for 5 years. We are concerned that clinical follow up (without ultrasound) in this patient group will fail to detect recurrent or residual multifocal tumours that are too small to be palpable on clinical neck examination. We would recommend that two two-yearly ultrasounds should be considered instead.	Thank you for your comment. The committee agreed there wasn't clear evidence on when and if ultrasound should be used after the initial follow up ultrasound. Therefore, they left it for the clinician to decide whether to do ultrasound at follow up reviews. We have added this to the rationale and updated the recommendation to state it is annual clinical follow up.

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Royal College of General Practitioners	General	General	General	Within this document, it is not clear where primary care fits within the pathway. It could be suggested that if a patient presents with a lump, then primary care should refer via a 2 week wait, or it could be interpreted that the GP should order an ultrasound scan and blood tests. We would request clarification on this as it should be noted that 30% of women regularly experience a swollen thyroid.	Thank you for you comment. The committee agreed diagnosis, treatment and follow up of thyroid cancer would be done in secondary care which makes it difficult to make the guideline applicable to primary care. NICE's guideline on thyroid disease (https://www.nice.org.uk/guidance/ng145) covers the earlier part of the pathway including recommendations related to investigating suspected thyroid dysfunction and thyroid enlargement, and treatment of non-malignant thyroid enlargement. The NICE guideline on suspected cancer (https://www.nice.org.uk/guidance/ng12) covers referral. We cross refer to both those guidelines at the relevant points in the thyroid cancer guideline.
Royal College of General Practitioners	General	General	General	General practitioners would welcome a separate NICE Guideline on thyroid masses if : • It included a statement that locally "14 Day Referral" templates should divide thyroid, throat, ear, other, neck masses into separation referral pathways. This guideline included a section on the presentation, assessment and referral of neck masses rather than only thyroid masses – the majority of patients present with "a lump in my neck" rather than "a lump in my thyroid"	Thank you for your comment. Thyroid masses are covered in section 1.2 on 'Investigating suspected thyroid dysfunction or thyroid enlargement' in the NICE guideline on thyroid disease (https://www.nice.org.uk/guidance/ng145) covers investigating lumps. The NICE guideline on suspected cancer (https://www.nice.org.uk/guidance/ng12) covers referral specifically for thyroid and separate from other head and neck cancers. We cross refer to both of those guidelines within our recommendations.
Royal College of	Guideline	014 - 015	017 - 005	Please could we request clarification as to who is responsible for thyroglobulin testing particularly if they have been discharged from surgical follow up? It is	Thank you for your comment. The committee agreed people with thyroid cancer are followed up in secondary care clinics where they remain the

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

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Stakeholder	Document	Page No	Line No	Comments	Developer's response
General Practitioners				difficult to work with absolute guidance on numbers in general practice as patients may disagree with the guidance recommendations and GPs work with a patient through a process of shared decision making. If this is the case, we would welcome so clarity regarding who holds the risk under these circumstances?	responsibility of the specialist team. In many places, GPs can't request thyroglobulin testing so this would be a barrier for discharging patients who need on-going thyroglobulin surveillance. The committee are not aware of people being treated by a GP.
Royal College of General Practitioners	Guideline-	General	General	Thyroid cancer is a relatively rare (though we recognise important) cancer for a general practitioner to see in primary care. Cancer Research UK quote 3865 new cases in a recent three period. This equates to a new case once every 5 years in a primary care practice of 10,000 (or around one case in every 25 years of practice for a general practitioner) hence this is not a case we are particularly familiar with. The guidelines emphasis that not all nodules are cancers (indeed in a primary care environment worth emphasising as we see many benign nodules), and the link with national resources (it might be worth being more specific if possible so that a generalist looking this up can find the resources easily). Otherwise, the documentation appears specific for a specialist community. The information on follow up is useful. We note there is not a great commentary on the population where the cancer is not amenable to treatment and wonder whether this is a conscious omission. During the end-of-life care situation with most cancers general practitioners and primary care	Thank you for your comment. The committee agreed diagnosis, treatment and follow up of thyroid cancer would be done in secondary care which makes it difficult to make the guideline applicable to primary care. NICE's guideline on thyroid disease (https://www.nice.org.uk/guidance/ng145) covers the earlier part of the pathway including recommendations related to investigating suspected thyroid dysfunction and thyroid enlargement, and treatment of non-malignant thyroid enlargement. The NICE guideline on suspected cancer (https://www.nice.org.uk/guidance/ng12) covers referral. Both those guidelines are cross referred to at the relevant points in the thyroid cancer guideline. The number of people not amenable to treatment or needing end of life care was not considered within the scope of this guideline and therefore we have not made any recommendations in this area. There is a NICE guideline on End of life care

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				play a significant role in symptom control and care in the community which should be emphasised.	(https://www.nice.org.uk/guidance/ng31) that covers all conditions.
Royal College of Nursing (RCN)	Guideline	General	General	We do not have any comments on this draft guideline. Thank you for the opportunity to contribute.	Thank you for your comment.
Royal College of Pathologists	Evidence review D	005	025	1.1.3 and throughout whole document The review question is... 'For people with thyroid nodules that require further investigation following ultrasound, what is the diagnostic accuracy of fine needle aspiration cytology (FNAC) with rapid on-site assessment, FNAC without rapid on-site assessment or core biopsy for diagnosing thyroid cancer. The guideline states 'consider using cytospin and cell block in addition to, or instead of smear when processing FNAC samples.' This statement is based on an extensive review of the literature in Evidence Review D. The cases are PIRO classified as follows FNAC without rapid on-site assessment (ROSA) with smear without cytospin and cellblock FNAC without ROSA with Cytospin and cell block, without smear. FNAC without ROSA with smear, cytospin and cell block FNAC with ROSA (by cytopathologist or technician) and with smear without cytospin and cell block FNAC) with ROSA (by cytopathologist or technician) and with smear with cytospin and cell block	Thank you for your comment. We have updated the wording in the recommendation, rationale and committee discussion in evidence review D to 'liquid based cytology' in response to your comment in the last paragraph on proprietary trademarks. The committee agreed that 'liquid based cytology' is a generic term that includes 'Cytospin and cell block' and is therefore more appropriate to use in a guideline recommendation.

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Core biopsy As 'Cytospin' is a trademark and is one of several cytocentrifuge techniques the wording throughout this document in the text where the term cytospin is referred to should be changed as described as shown: FNAC without rapid on-site assessment (ROSA) with smear without cytocentrifuge technique and cellblock FNAC without ROSA with cytocentrifuge technique and cell block, without smear. FNAC without ROSA with smear, cytocentrifuge technique and cell block FNAC with ROSA (by cytopathologist or technician) and with smear without cytocentrifuge technique and cell block FNAC) with ROSA (by cytopathologist or technician) and with smear with cytocentrifuge technique and cell block Core biopsy	
Royal College of Pathologists	Evidence review D	005	025	1.1.3 and throughout whole document Several of the articles cited in this section refer to *cytocentrifuge* techniques (referred to as *cytospin*) being used in addition to conventional FNAC. Some of the articles in Evidence review D describe specimens in which cell blocks are prepared, either via needle washings, or cytocentrifugation of a thyroid cyst fluid, and a much smaller number refer to cases where	Thank you for your comment. The committee agreed there is huge variation in practice across centres in the UK. Some of the large thyroid centres in the UK have discontinued preparation of direct smears and only use liquid based cytology for more than 10 years without any negative impact on diagnosis. Colloid can also be visualised on

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				cytocentrifuge specimens are made, without conventional direct smears. RCPath would comment as follows (i) Making a cytocentrifuge specimen without examining a direct smear is not performed in most laboratories, because direct smears are needed for diagnosis to readily identify thyroid colloid, which is a benign and clinically re-assuring feature. RCPath guidance would recommend making direct smears. Evidence suggests it is of limited value except in selected cases. (Edens J et al, Practical diagnostic utility of thyroid fine needle aspiration cell blocks : is always too much? J Am Soc Cytopathol 2021, Mar-Apr, (2), 164-167). (ii) If the whole specimen is processed for a cytocentifuge preparation as the draft guideline suggests when is says '*consider using cytocentifuge and cell block in addition to, or instead of smear when processing FNAC samples'* colloid is either lost or is more difficult to see. (iii) The evidence-based review D examines the rates of the various FNA diagnostic categories; Bethesda I-VI, Thy1-Thy5 etc. in patients who undergo surgery alone but it does not assess the rates of malignancy	well prepared liquid based cytology. The latter also offers excellent cell preservation and suitable material for ancillary testing. The committee, therefore, recommends either technique can be used. The committee agreed that it would be difficult to determine malignancy in people who did not have surgery. Therefore, they agreed that the gold standard to use when assessing evidence for diagnostic accuracy was surgical histopathological findings. They also noted that this is how diagnostic accuracy would be assessed in the evidence. There would be people in these studies with benign tumours who would be reported as **f**alse positives. Therefore, while not perfect the committee agreed that the evidence does provide evidence on diagnostic accuracy and the subsequent recommendations are based on the best available evidence.

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				in patients who have not undergone surgical excision. **(iv)** Evidence-based review D does not show robust evidence of the diagnostic accuracy of thyroid FNA for assessing benign lesions of the thyroid that have not undergone surgery as patients not undergoing surgery were excluded from the analyses. This is important because the recommendation to use cytocentrifuge techniques appears based on a relatively small number of publications whereas in day to day practice the guideline recommendations will then be applied to all thyroid FNAC. The efficacy of the FNA technique in this guideline is being assessed in relation to the diagnosis of potential cancer, not in the assessment of whether or not a given thyroid nodule is benign, as benign nodules do not undergo surgery. • **The RCPath notes that the established practice in most UK centres is to make cytocentrifuge preparations for those thyroid FNA's where there is a cyst fluid, or where there is sufficient cellular material remaining after making direct smears so that a cell block can be made if needed,**	

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

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Stakeholder	Document	Page No	Line No	Comments	Developer's response
				although frequently there is insufficient material to make or to attempt to make a cell block when there is a cyst fluid. • **The RCPath disagrees that cytospin prepations should be made in *preference* to or as a *replacement for* direct smears, because of the problem of visualising colloid in cytocentrifuge preparations for the diagnosis of benign thyroid lesions.** • **The preferred method would be that direct smears (both air dried and fixed) should be made to assess colloid and cellularity, with a liquid based cytology specimen from any needle washings if available and then a cell block only if there is any cytological material remaining after making direct smears and a liquid based cytology preparation. Cytocentrifuge/cytospin preparations and/ or cell blocks should only be made if needed for diagnosis following direct smear evaluation and if there is sufficient material.** See RCPath guidance https://www.rcpath.org/uploads/assets/b328ab3d-f574-40f1-8717c32ccfc4f7d8/G086-Tissue-pathways-for-diagnostic-cytopathology.pdf	

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Royal College of Pathologists	Evidence Review D	007		1.1.5.1 Why is Bethesda grading being used to capture evidence when the UK uses RCPath reporting terminology ?	Thank you for your comment. We included any data that used any established FNAC classification system. A variety of different systems were used in the included studies and these were meta-analysed according to the system used. Much of the evidence in the review is based on the Bethesda grading scheme which is why this is mentioned so frequently within the committee discussion of the evidence report. We also noted here that the Bethesda classification scheme is not commonly used in the UK. Therefore, the committee recommended that a Bethesda-equivalent scheme widely used in the UK called the RC PATH modification of the BTA (RC PATH BTA) should be used instead. The committee agreed that this uses qualitatively similar grades, whilst the main difference is fairly superficial, based on the labelling of each grade. RC PATH BTA grades Thy 1, 2, 3a, 3f, 4 and 5 are equivalent to Bethesda grades I, II, III, IV, V and VI respectively. We have added reference to the revised RCPath to table 3 of evidence report D.
Royal College of Pathologists	Evidence Review D	007	026 - 027	1.1.5.1 Line 26-27 'BTA' should read 'RCPath'	Thank you for your comment. We have amended this to revised Royal College of Pathologists (RCPath).

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

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Stakeholder	Document	Page No	Line No	Comments	Developer's response
Royal College of Pathologists	Evidence Review D	007	038 - 039	1.1.5.1 Line 38-9. "equivalent to Bethesda grades" - this UK document is rather Bethesda-heavy and could usefully include RCPath Thy classification as well at places such as this	Thank you for your comment. Bethesda is referenced a lot in the guideline because a lot of the evidence related to this system of reporting. We have included reference to the RCPath within the report. We acknowledge in the committee discussion (evidence review D) that much of the evidence in the review is based on the Bethesda grading scheme and that the Bethesda classification scheme is not commonly used in the UK.
Royal College of Pathologists	Evidence Review D	008 - 035	General	1.1.5.1 Table 2 Some of the references are very old, 1980s, how relevant are these today?	Thank you for your comment. The committee agreed that old data would still be relevant to this review. All papers were quality assessed to agreed processes. This point has been noted in the quality of evidence section in the committee discussion of evidence report D.
Royal College of Pathologists	Evidence Review D	008 - 035	General	1.1.5.1 Table 2 Some UK references appear to have been omitted, eg Newcastle have published a major series of correlation of thyroid FNA with histological findings but Parkinson D et al. J Clin Pathol doi: 10.1136/jclinpath-2016-204022 is not cited in the evidence based review	Thank you for your comment. We have checked this study and it would have been excluded due to type of FNAC not reported within the study.
Royal College of Pathologists	Evidence Review D	089	017	Table 22 "CB grades" in numerical numbers suggesting using Bethesda categories for core biopsies, this is not correct	Thank you for your comment. This is reported with roman numerals as that is how the study reported the results.
Royal College of Pathologists	Evidence Review D	098	001	Rec 1.1.13 The economic analysis assumes a scientific AfC band 4. To provide ROSA which is technically demanding if a clinical decision needs to be made in clinic whether	Thank you for your comment. The analysis has been amended to include the role of a cytopathologist. A recent RCPath survey on

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				to repeat the aspirate or perform needle core biopsy or discharge a patient it would require a consultant cytopathologist so the cost of ROSA needs to be revised in this costing. The examination using ROSA also requires a rapid direct smear technique, typically Diff-quick, to be examined in clinic and if necessary, with further direct smears and a cell block/cytocentrifuge if sufficient cytological material remains. **The cost stated of £38 per hour in 1.1.13 would therefore not be sufficient.**	cytopathology practice in the UK found a 50% split between BMS and pathologists among those performing ROSA. The calculation has been amended accordingly finding a cost of ROSA equal to £70, which is in line with other UK estimates.
Royal College of Pathologists	Evidence Review D	098	029	Rec 1.1.13 The baseline adequacy rate was derived from an evidence-based review, not a meta-analysis for Thy1 FNA, and this figure excluded cystic lesions Thy1c. The figures are not derived specifically from an RCPath publication, but rather from an evidence-based review that is misquoted. The correct reference is Poller DN et al Cytopathology;2020:31(6)502-508	Thank you for your comment and clarification. The in-text description and references have been amended. We looked at the study and could confirm that this figure does indeed include cystic lesion Thy1c. This figure was calculated from column 6 of table 4 reporting the overall percentage of Thy1. Only 3 studies in column 7 reports the proportion of Thy1c. The proportion of 18.5% was calculated across all studies in column 6 and, therefore, includes cystic lesions Thy1c.
Royal College of Pathologists	Evidence Review D	102	019 - 021	1.1.15.3 Lines 19-21 Please do not suggest use of 'cytospin and cell block' instead of referring to smears. Making a cytocentrifuge specimen without examining a direct smear first is not performed in most laboratories because direct smears are needed for diagnosis to readily identify thyroid colloid, which is a benign and clinically re-assuring feature. If the whole specimen is	Thank you for your comment. The committee agreed there is huge variation in practice across centres in the UK. Some of the large thyroid centres in the UK have discontinued preparation of direct smears and only use liquid based cytology for more than 10 years without any negative impact on diagnosis. Colloid can also be visualised on well prepared liquid based cytology. The latter also offers excellent cell

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				processed for a cytocentrifuge preparation as the draft guideline suggests when is says '*consider using cytospin and cell block in addition to, or instead of smear when processing FNAC samples'* colloid will be lost or is more difficult to see.	preservation and suitable material for ancillary testing. The committee, therefore, recommends either technique can be used. We have updated the wording in the recommendation, rationale and committee discussion in evidence review D to 'liquid based cytology' in response an earlier comment you made on proprietary trademarks. The committee agreed that 'liquid based cytology' is a generic term that includes 'Cytospin and cell block' and is therefore more appropriate to use in a guideline recommendation.
Royal College of Pathologists	Evidence review D	102	027	Rec 1.15.4 '*The additional cost of ROSA is estimated to be £28, 44 minutes of the hourly cost of a cytopathologist*.' As stated above, this should be recalculated to the cost of a **Band 7 clinical scientist or a medically qualified Consultant cytopathologist.** There is an apparent flaw in the costings as to undertake in-clinic reporting **requires in most situations at least a biomedical scientist band 4 to prepare and stain the smears, and also a consultant to interpret the smears**. The consultant if in clinic waiting for a specimen is unable to undertake other useful clinical work while waiting for the patient to be examined, the slides to be prepared and be stained by the biomedical scientist. A competency framework for BMS staff to undertake ROSA is being developed by the IBMS, as an	Thank you for your comment. The analysis has been amended to include the role of a cytopathologist. A recent RCPath survey on cytopathology practice in the UK found a 50% split between BMS and pathologists among those performing ROSA. The calculation has been amended accordingly finding a cost of ROSA equal to £70, which is in line with other UK estimates.

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				additional qualification at Specialist Portfolio level, and will be available in the very near future.	
Royal College of Pathologists	Evidence Review D	General	General	Whole Document **There is no separate stratification of cystic lesions (Thy1c or Thy2c) in this review.** This is important as most thyroid cysts on ultrasound are benign lesions. The criteria for Thy1 and Thy2 should therefore separate Thy1c and Thy2c as a Thy1c aspirate from a thyroid cyst indicates that the aspirate is not inadequate but in keeping with a benign cyst. Cystic lesions that are surgically excised are almost always removed because they are either suspicious clinically or on imaging or due to compressive symptoms. See existing RCPath Guidance on the reporting of thyroid cytology specimens (https://www.rcpath.org/uploads/assets/7d693ce4-0091-4621-97f79e2a0d1034d6/g089_guidance_on_reporting_of_thyroid_cytology_specimens.pdf). It should be noted that this guidance has been updated and has been through an RCPath consultation process. The basic Thy categories will be unchanged, although other aspects will be updated or expanded.	Thank you for your comment. Cystic lesions (Thy1c and Thy2c) are now explicitly distinguished in the recommendations. Thy1c was excluded from the recommendation on ROSE and was moved to a different row of the management table as neither ROSE nor CNB is considered appropriate for cystic lesions. Thy2c, has been spelled out in the table with the Thy2 recommendations. It was kept in the same row as the committee agreed that the current management for Thy2 is appropriate for Thy2c aspirates as well.
Royal College of Pathologists	Evidence Review D	General	General	Evidence-based review D examines the rates of the various FNA diagnostic categories; Bethesda I-VI, Thy1-Thy5 etc. in patients that undergo surgery alone. Review D does not assess the rates of malignancy in patients who have not undergone surgical excision.	Thank you for your comment. The committee agreed that it would be difficult to determine malignancy in people who did not have surgery. Therefore, they agreed that the gold standard

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Review D does not show robust evidence of the diagnostic accuracy of thyroid FNA for benign lesions of the thyroid that have not undergone surgery. The recommendation to use cytocentrifuge techniques is based on a relatively small number of publications. The efficacy of the FNA technique in this guideline is being assessed in relation to the diagnosis of potential cancer, not in the assessment of whether or not a given thyroid nodule is benign, as benign nodules do not undergo surgery. In routine day to day practice thyroid FNA is used as a test for both benign disease as well as also for cancer.	to use when assessing evidence for diagnostic accuracy was surgical histopathological findings. They also noted that this is how diagnostic accuracy would be assessed in the evidence. There would be people in these studies with benign tumours who would be reported as false positives. Therefore, while not perfect the committee agreed that the evidence does provide evidence on diagnostic accuracy and the subsequent recommendations are based on the best available evidence. Further detail has been added on this in the quality of the evidence section of the committee discussion in evidence report D.
Royal College of Pathologists	Evidence Review F	General	General	**Non RCT evidence should not have been excluded in the evidence review**. The purpose of diagnostic testing of thyroid FNA is for diagnosis of cancer versus a benign lesion in thyroid FNA. By excluding non-RCT evidence and not including non-RCT case/control studies almost all the available literature is excluded. Molecular testing requires the cytologist/pathologist to (i) view and report the FNA with a Thy class and then (ii) additional cellular material is sent for molecular testing (Thyroseq, Afirma etc). The molecular data can be analysed and reported by a laboratory blind to the knowledge of the Thy cytology result but these patients cannot be easily randomised in a trial as it would be very difficult to conduct a trial of molecular testing vs. no molecular testing as all the patients not receiving	Thank you for your comment. The committee noted that this is an area of interest with considerable potential impact on future practice. The committee agreed that there were few molecular tests available in the UK and that without high quality randomised controlled trials (RCTs) demonstrating their cost-effectiveness they would not recommend them. There weren't any RCTs in the area so the committee have made a research recommendation to address this question. "For people who have had fine-needle aspiration samples, where the FNAC sample was adequate but was not able to differentiate between benign and malignant samples, what is the clinical and cost effectiveness of molecular testing?" Please see Appendix J in Evidence review F for further details.

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				molecular testing on the first occasion would require a repeat ultrasound guided FNA perhaps 3-4 weeks after the first FNA with the cost and ethical issues of a second FNA or core biopsy procedure undertaken for purely research purposes. That is why there is no RCT evidence in the literature. The guideline also ignores some of the other benefits of molecular testing, eg that if certain mutations are present eg BRAF V600E it implies a 99.9% certainty of the presence of thyroid carcinoma whereas the risk of malignancy of a Thy5 FNA for cancer is in the region of 97-99% This may be helpful if extensive surgery is planned such as lateral neck dissection and pre-operative confirmation of malignancy cannot be achieved via other means, if BRAF V600E result shows a mutation. If an Afirma result is negative, the risk of malignancy for a thyroid lesion is below 5%, hence giving reassurance to the patient that an operation is usually not needed The use of molecular testing of all newly diagnosed thyroid cancers is now routine via the NHS England Genomic Hubs as it is of value in selecting targeted therapies for relapsed iodine refractory thyroid cancer	The committee do not think that an RCT would be difficult. The research question focuses on comparing molecular tests to usual care in people with indeterminate results. If these guideline recommendations are implemented then usual care would be compared to repeat sampling with FNAC or core needle biopsy, or diagnostic hemithyroidectomy. We will flag the inclusion of diagnostic accuracy data to NICE surveillance team for consideration when the guideline is updated. BRAF testing to distinguish benign lesions would not be considered for this evidence review as it is not part of a diagnostic treatment. The committee do not agree that molecular testing as part of diagnostics, prior to surgery, is routinely used in the UK. The guideline review only assesses molecular testing as a diagnostic technique before any surgery (including diagnostic) is undertaken. They agreed that they may be used as part of the treatment pathway in selected cases where there are metastases outside the neck.
Royal College of Pathologists	Guideline	005	008	Rec 1.1.2 The guideline states that '*Core biopsy follows the RCPath FNAC classification system'*	Thank you for your comment. The committee agree and that statement has been removed from the introduction (section 1.1.2) of evidence report D. We

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				This statement is misleading and needs rewording. The RCPath Tissue Pathways for Endocrine Pathology published in 2019 states in the last paragraph of page 9 that ***'It may be helpful to categorise core biopsies in a manner similar to those used for thyroid cytology'*** **but RCPath does not specifically state how to report CNB of the thyroid** so the statement above is not accurate. There is no agreed international or UK reporting terminology system for reporting needle core biopsies of the thyroid gland because the inherent problems of thyroid needle core biopsy interpretation. There is a Korean NCB reporting terminology system, (see Na DG et al. Korean J Radiol 2017;18:217-237) but it is not used in the UK as it has multiple indeterminate categories with low levels of inter-observer agreement and reproducibility. Microsoft Word - G078 Tissue pathways for endocrine pathology For Publication.docx (rcpath.org)	cannot see this statement anywhere else within the guideline.
Royal College of Pathologists	Guideline	007	005	Rec 1.2.12 The RCPath has major concerns about widespread implementation of cytocentrifuge/cytospin techniques for **all** thyroid FNA specimens as the draft guideline appears to suggest and we feel that this wording is inappropriate. Well prepared direct smears (MGG and Papanicolaou) are considered crucial in the interpretation of FNA aspirates by most	Thank you for your comment. The committee do not agree that cytospin or cell blocks should not be used when processing FNA samples. However, they do agree that there was not enough evidence to recommend one method over the other. Therefore, the recommendation has been amended to state. 'Use

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				cytopathologists so we disagree with the wording **"Consider using cytospin and cell block in addition to, or instead of, smear when processing FNAC samples".** We would replace it with **'Well prepared direct smears (both air dried and fixed) are preferred for diagnostic purposes. For FNAC consider using a cytocentrifuge technique with cell block if sufficient cytological material is present after examination of direct smears'** (i)Smears are essential for evaluating colloid which is the most useful indicator of benign pathology in thyroid lesions. This is lost completely or very poorly seen in cytocentrifuge/cytospin preparations and in cell block preparations. In addition to loss of background, architecture is also lost in cytocentrifuge/cytospin preparations and cells are seen in 3 dimensional groups making visualization & interpretation difficult. It should also be borne in mind that in a correctly spread and stained cytology smear 100% of the cellular material is available for examination. This is in contrast to a cell block where a section typically of 5 micron thickness from a block of 3mm thickness would only represent some 0.17% of the available material potentially. (ii) Diagnostic criteria for diagnosing lesions on FNA are based on a 2 dimensional artefact created by the smearing process used in the making of direct smears.	liquid based cytology, direct smear or both when processing FNAC samples.' The wording in the recommendation has been updated to 'liquid based cytology' in response to your comment in the last paragraph on proprietary trademarks. The committee agreed that 'liquid based cytology' is a generic term that includes 'Cytospin and cell block' and is therefore more appropriate to use in a guideline recommendation. (i) the committee agreed that colloid can also be visualised on well prepared liquid based cytology. (ii) the committee agreed that architectural details are better seen on a direct smear, however, liquid based cytology offers excellent cell preservation and suitable material for ancillary testing such as immunohistochemistry and molecular testing. (iii & iv & vi) The committee recognise that different centres handle this differently. A review on how to process the specimen was not included as part of the guideline and that level of detail is not included as part of the guideline. (v) the recommendations for ROSA are based on the clinical and cost effectiveness evidence we identified. A threshold analysis identified our cost comparison

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Universal use of cytocentrifuge/cytospin techniques can increase the indeterminate FNA rate by removing background & architectural details, concentrating & compressing cells and tissue fragments into a smaller area and also making interpretation difficult. (iii) Patients would be better served if the guideline emphasized that **'Good quality fixed and air dried direct smears should be prepared at source for Papanicolaou and MGG staining respectively'**. Provision of good quality cytologic material is the cornerstone of diagnostic practice and would not only reduce the inadequate rate but also the indeterminate rate. Overall diagnostic accuracy and reproducibility would be ensured if compliance with this particular factor can be ensured rather than trying to use cytocentrifuge/cytospin and CNB as an aid to compensate for the lack of good quality smears. It should be emphasized that this well known within the pathology community but it is often not understood by other clinicians and aspirators. (iv)Both stains PAP and Romanowsky are essential in making a diagnosis of thyroid lesions especially thyroid cancer and distinguishing between types of thyroid cancer. Both provide complementary information to each other - something that cannot be fully reproduced in cytocentrifuge/cytospin preparations. This is highlighted in the College guidance *Tissue Pathways*	analysis would be relatively similar threshold identified by the Royal College of Pathologists (>15%) when Thy1c is excluded. Therefore the committee agreed to use a threshold of >15% in the recommendation.

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				for diagnostic cytopathology dated October 2019, G086 , section 3.2 (https://www.rcpath.org/uploads/assets/b328ab3d-f574-40f1-8717c32ccfc4f7d8/G086-Tissue-pathways-for-diagnostic-cytopathology.pdf). (v) Centers in the UK such as Guy's and St Thomas's in London which have implemented good quality direct smears (MGG and Papanicolaou) with biomedical scientist or pathologist ROSA have consistently been able to achieve Thy1 rates well below 10% with high diagnostic accuracy rates without the need to make use of cytocentrifuge/cytospin techniques, or cell blocks or CNB, (personal commication Dr M Moonim and Dr A Chandra). (vi) Cell blocks are not useful in the diagnosis of benign follicular lesions as there is overlap in the morphologic spectrum of non-neoplastic & neoplastic follicular lesions. The same applies to core needle biopsy including the further disadvantage that CNB may create histopathological artefacts which can simulate malignancy in follicular lesions – an issue which needs to be emphasized. The forthcoming 2022 RCPath Thyroid Cancer Dataset and the British Thyroid Association Thyroid Nodule guidelines currently in preparation advise against using core needle biopsies except in very selected situations, eg	

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				after (>=2) repeat Thy1 FNA and for a few other selected indications. '**Cytospin' is a proprietary trademark and it is only one of a number of methods to make cytocentrifuge preparations**. The document refers to fine needle aspiration cytology (FNAC) and cytocentrifuge techniques which may include cytospin TM. *'Cytospin'* is a UK trademark owned by Thermo Shandon Ltd, Astmoor, Runcorn, Cheshire, WA7 1PR and it is also registered at the US Trademark Office number 3003724 to Thermo Electron Corporation Delaware, 47770 Westinghouse Drive, Fremont, California, 94539, USA and in other jurisdictions also. **Hence throughout the document the word '*cytospin*' if it is to be used it should be replaced by the phrase '*cytocentrifuge technique'*** as there are a number of other methods to make thyroid FNA cyto-centrifuge preparations that are equally effective and which do not require the use of Thermo Shandon laboratory equipment. The fact that the term '*cytospin*' is used in multiple peer reviewed publications without making it clear that it is a proprietary trademark is an oversight in the peer reviewed publications	
Royal College of Pathologists	Guideline	007	005	Rec 1.2.12 **There is no discussion in the guideline or review of the evidence of liquid based cytology (LBC) specimens for diagnosis of cancer by thyroid FNA. This is a significant omission.**	Thank you for your comment. The wording in the recommendation has been updated to 'liquid based

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				The RCPath would also like to clarify (i) Is the term 'cytospin' as currently used in this draft NICE guidance also intended to refer to liquid based cytology specimens (LBC)? If so this is incorrect. An LBC specimen is very different to a cytopsin and the two must be identified separately. The comments in point 1 above refer to cytopsin specimens, and not an LBC sample. (ii) What is the meaning of the term 'smear' in this guideline? Does 'smear' mean just directly made FNAC smears or does it include liquid based cytology preparations? (iii) Does the guideline need to refer to the specific stains to be used? eg May Grunewald-Giemsa and Papanicolaou or if not at least reference a document that describes the relevant stains, eg The Royal College of Pathologists Guidance on the Reporting of Thyroid Cytology specimens? (iv) **T**he interpretation of LBC techniques is slightly different to direct smears. In LBC specimens the cells shrink slightly due to fixation effects, and thyroid colloid is more difficult to see compared to conventional	cytology' in response to your comment on proprietary trademarks in the last paragraph. In response to your points: (i) The committee agreed that 'liquid based cytology' is a generic term that includes 'Cytospin and cell block' and is therefore more appropriate to use in a guideline recommendation. (ii) & (iv) The word 'smear' has been updated to 'direct smear' to reflect that it means directly made FNAC smears and not liquid based cytology. (iii) The review protocols didn't include the types of direct smears and therefore the committee has avoided making reference to specific stains used in the guideline. The recommendation has been updated to 'Offer liquid based cytology, direct smear or both when processing FNAC samples.' These changes have been made to the recommendations, rationale and committee discussion of evidence report D.

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				direct smears stained with Papanicolaou or Giemsa. The omission of any discussion on LBC techniques in this guideline is a major oversight and we feel needs to be corrected**.** Liquid-based cytology (LBC) is claimed to have a diagnostic sensitivity as accurate as conventional smear preparations with excellent cell preservation and the lack of background material on LBC can decrease the number of inadequate diagnoses. The cellular material stored in preservative solution can also be used for the application of immunocytochemical and molecular techniques. The cytologic features are similar to conventional smears but thyroid colloid, lymphocytes and nuclear detail are more easily evaluated in direct smears whereas nuclear details only are better evaluated in LBC slides. Rossi et al. Front. Endocrinol., 16 May 2012 | https://doi.org/10.3389/fendo.2012.00057	
Royal College of Pathologists	Guideline	007	005	Rec 1.2.12 The guideline states, 'consider using cytospin and cell block in addition to, or instead of smear when processing FNAC samples.' This statement is based on an extensive review of the literature in Evidence	Thank you for your comment. The committee do not agree well prepared direct smears are preferred over cytospin or cell blocks. However, they do agree that there was not enough evidence to recommend one method over the other. Therefore, the

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Review D. This statement could be more appropriately modified to '**Well prepared direct smears (both air dried and fixed) are preferred for diagnostic purposes. For FNAC consider using a cytocentrifuge technique with cell block if sufficient cytological material is present after examination of direct smears'.** See points made above.	recommendation has been amended to state. 'Offer liquid based cytology, direct smear or both when processing FNAC samples.' The wording in the recommendation has been updated to 'liquid based cytology' in response to one of your other comments that 'Cytospin' is a proprietary trademark and there is now reference to liquid based cytology in the recommendations. The committee agreed that 'liquid based cytology' is a generic term that includes 'Cytospin and cell block' and is therefore more appropriate to use in a guideline recommendation.
Royal College of Pathologists	Guideline	007	009	Rec 1.2.14 Rephrase as it is uncertain what is meant by a 'period of ROSA'? If it needs to be put in place, would it not have to be on going? Rephrase this so that this recommendation refers only to aspirates that are Thy1 so that it does not include Thy 1c (cystic) aspirates.	Thank you for your comment. The mention of the "period of ROSA" has been removed from the recommendation. The recommendation has also been amended to exclude Thy1 (cystic) aspirates.
Royal College of Pathologists	Guideline	007	009	Rec 1.2.14 Please state that Thy1c.aspirates should be excluded	Thank you for your comment. The recommendation has been amended to exclude Thy1c (cystic) aspirates.

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Royal College of Pathologists	Guideline	007	014	Rec 1.2.15 Table 1 should be amended to left to corner to read 'Thy1 (inadequate) excluding Thy 1c aspirates' in the recommendations: -Thy1 – Offer repeat FNA in the first instance and correlation with USS. CNB should be offered only after repeated THY1s (> 2) if high risk by US criteria. This is not an option for indeterminate lesions by either BTA / TIRADS. -Thy1c – this category is not addressed at all -Thy2 and 3a - emphasis is on CNB rather than repeat FNA. Usual practice both in the UK and in most overseas centres would be to suggest FNAC first with CNB as second option. CNB should not be used in the evaluation of low risk lesions or solitary U3 lesions. -Thy3a has no mention of reading the words to see what sort of atypia it is. IN fact, everywhere the categories are used as stand-alone diagnoses; within the Thy3a category there are 4 main subtypes of FNA; scanty atypia (SA), scanty microfollicular (SMF), favour benign (FB), and thyroiditis versus neoplasm (TVN), see van der Horst et al. Cytopathology 2020 https://doi.org/10.1111/cyt.12910 -Thy4 and 5 should be dealt with separately not on the same row, they are different, the risks of malignancy are different and the clinical management is different.	Thank you for your comment. The management of Thy1c has been added as an additional row as suggested. -Thy1 (excluding Thy1c) – The committee do not agree that FNAC should be repeated in the first instance. Both CNB and FNAC with ROSE were shown to improve accuracy, prevent new Thy1 aspirates. Furthermore, CNB was shown to be cost-effective for repeat sampling. The recommendations have been updated to make this clearer so that both CNB and FNAC with ROSE are the first choice, with FNAC alone being an option if those are unavailable or inappropriate**.** This provides flexibility to the centres that may have only one available. - Thy1c – the committee agree this needs a separate row. They recommend repeating FNAC. If the second FNAC is also Thy 1c and the ultrasound appearances are concerning, diagnostic hemithyroidectomy should be considered. - Thy2 and Thy2c – the committee agree that FNAC should be offered first and have amended the recommendation to reflect this. They do not agree that CNB should not be used for Thy2 and Thy3a. It can be useful as it extracts more material.

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				-column 1 says "(indeterminate)" for both Thy3a and Thy3f but should be "atypical, neoplasm possible" and "atypical, follicular" -there is no recommendation for MDT discussion in the table or in the accompanying text -There is no mention in this document as to the type of needle to use if repeated THY1s are obtained. Guidance should mention use of 27G needles and use of lignocaine with adrenalin to cause vasospasm and allow good access with institution of ROSA if necessary. Use of thicker gauge needles (usually 23G blue needles) invariably produces haemorrhagic and THY1 aspirates.	- Thy3a – The committee agreed that CNB was the preferred approach as this reflected the findings of the economic evaluation and clinical review. They have, however, softened the recommendation to a consider. This will allow flexibility in the cases CNB is unavailable or inappropriate. - Thy4 and Thy5 are grouped together in this table as the recommendations are the same. The table only covers recommendations related to diagnosis and not further management. The column labels were corrected for Thy3a and Thy3f as suggested. The effectiveness of MDTs was not looked at in the guideline and therefore there are no comments on them. The recommendations are made on the basis of what to do regardless of the involvement of the MDT although the committee assume that MDTs are involved in a lot of decisions about care. The literature review did not look at the effectiveness of different needles or lignocaine with adrenaline in FNAC so the committee could not make a specific recommendation on this matter.
Royal College of Pathologists	Guideline	007	014	Rec 1.2.15 **THY2 (benign).The RCPath disagrees with the conclusion of the draft guideline about the**	Thank you for your comment.

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				recommendation for the use of CNB for reassessment of lesions with THY2 cytology. (i)The management option should be reassessed and rephrased. The specificity of a THY2 diagnosis on cytology is >97% while the specificity of a U5 is <60% and that of a U4 less than this. Therefore cytology is superior to US and the management should be amended as they are currently incorrect. If a lesion is Thy2 and US low risk there is no value to repeating the FNA or performing CNB. (ii) U3 lesions either solitary or particularly in the context of multinodularity do not require repeat FNA if a THY2 diagnosis is achieved. Discharge to GP or US surveillance if patient is anxious or surgery if the patient is symptomatic would be appropriate options. **(iii)** The recommendation for U4/U5 lesions with THY2 cytology should be to first review US in the MDT and only if high risk should a repeat FNA be offered. CNB should not be utilized as a first option here.	The committee agree that CNB shouldn't be the first choice for repeat sampling in Thy2. However, they also agree it should have less emphasis in the recommendations. CNB is still mentioned as an alternative to FNAC if there is clinical concern. The recommendation states that FNAC should be repeated only if the US continues to reach the threshold of FNAC. This may usually be U3 – U5 but the committee have not stated this as they do not recommend a particular classification system. People with low-risk nodules on the repeated ultrasound will not be required to repeat FNAC. People with concerning US findings may still be required to repeat FNAC but CNB is no longer recommended as a first option. The committee agreed this is in keeping with current practice. The recommendations are consider recommendations to reflect the uncertainty in the evidence base.
Royal College of Pathologists	Guideline	007	014	Rec 1.2.15 **Management option, sentence 3 needs rephrasing. CNB should not be utilized as first option here.** This should read ' Discharge people if their FNA results are benign ….'.	Thank you for your comment. The recommendation has been amended to consider FNAC first if the second ultrasound continues to reach the threshold for FNAC. CNB can be considered as an alternative to FNAC.

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					Discharge is recommended for people with a benign FNAC once the benign status is confirmed. the committee recommend considering a repeat FNAC only if the second ultrasound reading is concerning.
Royal College of Pathologists	Guideline	007, 028, 029 and 030	014	Rec 1.2.15 Various lines **The recommendation to use core biopsy CNB if the 1st FNA is Thy1 or Thy3a is problematic**. (i)Thyroid needle core biopsy is a more complex and risky procedure than FNA, with a higher rate of complications. The RCPath agrees that CNB has a role in managing repeat assessment of thyroid nodules if multiple FNA (at least 2) are Thy1 provided also that the lesion is high risk on US. (ii) RCPath would prefer that the FNA is repeated after the first Thy1 or Thy3a (with all the guidance on type of needle etc mentioned above put in place) rather than proceeding directly to CNB in the event of Thy1 or Thy3a. **(iii)** CNB does not help in the diagnosis of follicular lesions (>90% of all thyroid nodules sampled). CNB is unable to discriminate between a benign vs. malignant follicular lesion (iv)CNB produces artefacts which simulate malignancy in follicular lesions on histological assessment of subsequent resections. The recommendation for use of CNB risks leading to many additional cases of	Thank you for your comment. (i) CNB is more complex and expensive than FNAC. This was explicitly considered both in the health economic analysis, where CNB had a higher procedural cost, and in the recommendations where FNAC is recommended in all cases where CNB seems inappropriate (for instance when the nodule is close to a blood vessel). The committee agreed that CNB is in general considered a more risky procedure than an FNA, but safe in hands of experienced radiologists who are happy to do the procedure except when it is inappropriate. (ii) After a Thy1, both CNB and FNAC with Rapid On-Site Evaluation (ROSE)/Rapid On-Site Assessment (ROSA) were found to be effective in reducing the possibility of receiving an additional Thy1. The committee agreed that these would be expected to reduce repeat Thy1 and therefore the need of diagnostic surgeries. The recommendations have been updated to make this clearer so that both CNB and FNAC with ROSE are the first choice, with FNAC

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				thyroid lesions which will be diagnosed as minimally invasive follicular carcinoma due to biopsy artefacts as pathologists are unable to reliably discriminate between what is an artefactual capsular invasion caused by a CNB and what is genuine capsular invasion on subsequent resections. This will be reflected in forthcoming guidance from both the British Thyroid Association and the Royal College of Pathologists where very selected indications for thyroid core biopsy are specified (to be published shortly). (v)This draft NICE guideline has not taken into consideration in the evidence based review the reduction in THY1 rates and improved diagnostic accuracy (reduction of THY3A rate) seen in centres where 27G needles are used for Thyroid FNA and where lignocaine with adrenalin is used for vasospasm and better needle access in thyroid nodules with significant peripheral vascularity. (vi)The guideline has not taken into consideration in the evidence-based review the scenario that if ROSA is widely implemented for centres with higher (>15% Thy1 rates excluding Thy1c aspirates) **repeat FNA can be performed in the in-clinic setting so that often a Thy1 can be most often resolved to other Thy categories without a need for CNB.**	alone being an option if those are unavailable or inappropriate. CNB was also found to be more cost-effective than FNAC after Thy3a, and a consider recommendation was made to allow for alternative options if CNB is not appropriate. The committee agreed that where follicular lesions are suspected this would be categorised as Thy3f and not Thy3a. (iii) The committee agree that neither CNB nor FNAC is helpful in the diagnosis of the follicular lesions. The recommendation for suspected follicular lesions (Thy3f) does not mention any form of repeat biopsy recommending, instead, diagnostic hemithyroidectomy as the only way to discern benign and malignant follicular lesions. (iv) The issue of artefacts left by CNB or FNAC is well known by the committee. Expert members of the committee agreed that CNB can, in some cases, leave "larger" artefacts due to the larger size of the needle, but in their clinical experience never had any issues when discriminating real lesions from artifacts. This further discussion was added to the committee discussion section of evidence report E. The committee did not agree that this issue would make the use of CNB inappropriate in England.

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				(vii) The guideline in the evidence base review also takes no account of the fact that most of the published data on thyroid needle core biopsy of the thyroid is from Korea. The incidence and practice of thyroid nodule assessment in Korea is significantly different to that in Europe, North America, and in the UK. Korea practices thyroid screening ultrasound and the incidence and prevalence of thyroid cancer, specifically papillary thyroid cancer in Korea from publications is higher than in the UK based on published evidence. The 'epidemic' of thyroid cancer in South Korea is attributed to US screening, see Park S at al. Association between screening and the thyroid cancer "epidemic" in South Korea: evidence from a nationwide study https://doi.org/10.1136/bmj.i5745**.** and Ahn et al NEJM 2015;373:24:2389-2390 **(viii)There is also evidence that the results achieved for thyroid FNAC are different between centres in Asia, and those in the Europe, North America and the UK** as showing in a recent meta-analysis by Vuong et al '*Differences in surgical resection rate and risk of malignancy in thyroid cytopathology practice between Western and Asian countries: A systematic review and meta-analysis'*. Cancer Cytopathology 2020;128:238-249. Compared with Asian practice, western series had a significantly lower risk of malignancy in most of Bethesda categories, whereas the resection rate was not	(v) The evidence review protocol did not compare FNAC done with different kind of needles and therefore we have not made recommendations in this area. (vi) Both CNB and FNAC with ROSE were shown to improve accuracy and prevent new Thy1 aspirates. Furthermore, CNB was shown to be cost-effective for repeat sampling in the health economic analysis. The recommendations have been updated to make this clearer so that both CNB and FNAC with ROSE are the first choice, with FNAC alone being an option if those are unavailable or inappropriate**.** This provides flexibility to the centres that may have only one available. ROSE is not helpful after Thy3a, so its use is not recommended after that cytology. A separate category has also been added for Thy1c where the committee agreed that FNAC should be repeated, and if the second FNAC is also Thy 1c and the initial ultrasound appearances are concerning then diagnostic hemithyroidectomy should be considered. (vii) The committee do not agree that most of the evidence on CNB is from South Korea. The meta-analysis (Pyo 2016) that was used to assess accuracy of CNB and FNAC as repeat test after a Thy1 or a Thy3a aspirate includes 26 studies. Of these, only half were conducted in South Korea with the remaining half

				statistically different. Focusing on indeterminate nodules, the resection rate in Western series was significantly higher (51.3% vs 37.6%; P = .048), whereas the risk of malignancy was significantly lower (25.4% vs 41.9%; P = .002) compared with those in Asian series.. This implies that the UK cannot rely on Korean data without looking at first our own experience. In the UK there is only one centre that has published a significant series of patients managed by CNB (the same centre also uses FNA for some but not all patients). This centre showed a Thy1 rate of 45.3% and of 551 patients operated, 149 (27%) were Thy1 and 39 (7%) were Thy1c. See Appukutty SJ. et al J Clin Pathol 2021;0:1-7. In the same centre 7.2% of the core biopsies were inadequate (T1) and 59.3% were indeterminate (T3). 16.5% of the core biopsies were performed after a previous FNA, while 83.5% were performed as the initial diagnostic procedure. **Therefore, it can be inferred that the inadequate rate of CNB (T1) in the UK is not very different to the expected rate of Thy1 (8.5%) if FNAC is performed with ROSA (Poller DN et al Cytopathology;2020:31(6)502-508) and it does not indicate that CNB is superior to FNA in its diagnostic accuracy.** (ix)The subclassification systems for core biopsy used by Korean pathologists for reporting needle core	being European or US studies. Although South Korea may differ in practice and incidence, this is not expected to affect or invalidate studies looking at the accuracy of repeat tests done in people with a previous Thy1 or Thy3a aspirate. (viii) The committee agree that there are differences between western and Asian countries such as those reported in Vuong. This is why the risk of malignancy in all RCPath categories included in the model was informed from a UK meta-analysis (Poller 2020). Hence, the economic analysis is not overestimating prevalence of cancer in the UK. A potentially higher prevalence of cancer in Thy1 and Thy3a aspirates in the Korean studies included in the meta-analysis is not expected to affect or invalidate the accuracy of repeat FNAC or CNB estimated by the meta-analysis. The recommendation for Thy1 has been updated to offer repeat sampling CNB or FNAC with ROSE as the first choice. (ix) The Cambridge Group Study confirms that both FNAC and CNB are suitable initial tests for the evaluation of thyroid nodules. The study did not attempt to compare the usefulness of repeat FNAC vs CNB after a Thy1 and Thy3a, so it cannot be used to infer whether one is more useful than the other as a second-line test. The committee agree that CNB is more expensive and technically complex and should be used where it is

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

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Stakeholder	Document	Page No	Line No	Comments	Developer's response
				biopsies are also not directly applicable to the UK. The Cambridge group (Appukutty SJ. et al J Clin Pathol 2021;0:1-7) reported 305 of 514 cases as T3 (follicular lesion with architectural or cytological atypia) equivalent to Thy3a/Thy3f. **The RCPath therefore does not support the conclusions of the draft guideline that CNB is superior to or should be used in preference to repeat FNAC for Thy1 lesions that are not Thy 1c** **We also disagree with the draft guideline conclusion that CNB will improve NHS efficiency and reduce overall costs. It is likely that widespread use of CNB will actually increase NHS costs as**: 1.core biopsies are inconclusive in all follicular lesions (>90% of all thyroid lesions) 2.Widespread use of CNB will likely increase the number of surgeries due to more inconclusive CNB results 3. The greater cost of the core biopsy in these patients in addition to cost of subsequent diagnostic / therapeutic surgery and invariably a slower turn around time also 4. There will be a cost of managing the additional cases that may be diagnosed as minimally invasive follicular thyroid carcinoma due to the problems of assessment of CNB and capsular invasion	most useful: after a Thy1 (excluding Thy1c) or Thy3a aspirate. These recommendations are supported by the health economic and clinical evidence. However, the committee were aware that there is heterogeneity in practice with some centres preferring FNAC with ROSE so the recommendation was made to include FNAC with ROSE as a valid alternative to CNB for the management of people with Thy1. The committee disagree with the conclusion of this comment. They agreed that: 1. CNB is not recommended after suspected follicular lesions (Thy3f) so there will not be an increase in inconclusive aspirates in follicular lesions 2. CNB has been demonstrated to produce fewer inconclusive results compared to repeat FNAC, so it is expected to reduce the number of surgeries 3. Despite being more expensive than FNAC, the economic model found benefits of CNB to offset its initial cost therefore demonstrating it is cost effective. **4 Artefacts caused by CNB or FNAC are expected to cause minimal impacts as expert members of the committee confirmed that a trained histopathologist can distinguish a malignant lesion from an artefact.**

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Royal College of Pathologists	Guideline	019	General	Table 3 Typo in description of THY3A and F: it should be neoplasm rather than neoplasms.	Thank you for your comment. We have corrected the typos.
Royal College of Pathologists	Guideline	027	006 - 008	The evidence review showing value of FNA with cytocentrifuge/cytopsin and cell block showing high sensitivity (0.937) and specificity (0.825) for identification of nodules as Bethesda Class 3 or above is based on a very small number of published articles (5 studies only). There is a real risk of bias in this conclusion given that this recommendation is only based on 5 studies albeit 1000 plus patients. It is standard practice in **almost all centres if a thyroid nodule is cystic to make a cell block from the FNA material with a direct smear or a cytocentrifuge/cytospin from the cyst content**s but frequently is not mentioned in the methodology in published articles as this is assumed to be normal good clinical practice.	Thank you for your comment. The committee agree that there was not enough evidence to recommend one method over the other. Therefore, have amended the recommendation to state. 'Offer liquid based cytology, direct smear or both when processing FNAC samples.' We have updated the wording in the recommendation to 'liquid based cytology' in response to one of your other comments on proprietary trademarks. The committee agreed that 'liquid based cytology' is a generic term that includes 'Cytospin and cell block' and is therefore more appropriate to use in a guideline recommendation.
Royal College of Pathologists	Guideline	027	020 - 021	There is no requirement for cytospin and cell block if smears are properly made and stained. Many major centers do not use a cytospin technique and rely on smears only with a cell block *if necessary* with excellent diagnostic results.	Thank you for your comment. The evidence favoured cytospin and cell block however, committee agree that this was not enough to recommend one method over the other. Therefore, the recommendation has been amended to state. 'Offer liquid based cytology, direct smear or both when processing FNAC samples.' the wording in the recommendation has been updated to 'liquid based cytology' in response to one of your other comments on proprietary trademarks. The

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

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					committee agreed that 'liquid based cytology' is a generic term that includes 'Cytospin and cell block' and is therefore more appropriate to use in a guideline recommendation.
Royal College of Pathologists	Guideline	028	021 - 031	The recommendation here to resample THY2 nodules is at variance with most other guidelines as we moved away from resampling THY2 nodules several years back. Since then, in routine practice the incidence of false negative THY2 is exceptionally rare.	Thank you for your comment. The committee's consensus was that the recommendations are similar to some current guidelines, and it would be a change in current practice without clear evidence of benefit to move away from this.
Royal College of Pathologists	Guideline	029	008 - 009	It begs the question as to how repeat sampling is less useful in THY3F, considering that the most common histological outcome for a THY3F nodule is a multinodular goitre/ benign follicular lesion. In patients with multinodular disease THY3F cytology is a false positive diagnosis in most patients and largely reflects the way a FNA has been performed (operator dependant) or a characteristic in the growth pattern of a goitrous / adenomatoid nodule.	Thank you for your comment. The committee agreed that for suspected follicular lesion (Thy3f), repeat sampling with FNAC or CNB is less useful as they are unable to discriminate between benign and malignant follicular lesion. Hence, the committee agreed that diagnostic hemithyroidectomy is justified in this category, taking into account their high risk of malignancy (around 30%). There were also concerns that, if not followed up with surgery, final diagnosis after Thy3f could take longer to happen. This would delay treatment for a potentially malignant tumour, create uncertainty for the person, and in some centres lead to a longer delay than is allowed by NHS cancer targets. The recommendation is a 'consider' recommendation because the committee agreed is uncertainty in the evidence. Molecular testing may be an option for the future in Thy3f disease however currently there wasn't

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

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Stakeholder	Document	Page No	Line No	Comments	Developer's response
					the evidence to recommend it and a research recommendation was made. The committee have relabelled Thy3f from 'indeterminate' to 'suggesting follicular neoplasm' to reflect the Royal College of Pathologists terminology. The committee have updated the rationale to reflect this uncertainty and further detail can be found in the committee discussions of Evidence report E and D and the research protocol for molecular testing is in evidence report E.
Royal College of Pathologists	Guideline	029	020 - 024	The guideline comments that molecular tests are largely unavailable in the NHS and are mostly produced outside the UK but the NICE process for evaluation of new diagnostic tests is to undertake a NICE diagnostic technology appraisal. Why was this not suggested in the draft guideline? It is also possible to assess the usefulness of a diagnostic test without using RCT evidence	Thank you for your comment. The scope of this guideline did not include doing a diagnostic technology appraisal as this follows a different process. We have made research recommendations for molecular testing in the hope that more evidence will be available in the future for any guideline update.
Royal College of Pathologists	Guideline	029	026 - 27	The language has changed - ' if there are clinical concerns' This wording needs to be reflected in table 1 where phrasing is very unclear.	Thank you for your comment. We have updated this sentence to state 'The recommendation to consider repeat ultrasound and repeat FNAC with Thy2 reflects current practice and it is not expected to have an impact on NHS resources.'
Royal College of Pathologists	Guideline	029 -030	026 - 006	Any change in practice will also have an impact on Pathology staff, especially at senior BMS and Consultant Pathologist level. Any change from FNAC to CB will require education and training and also	Thank you for your comment.

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				resourcing of laboratory practice in sample handling and reporting. It is unclear why impact on Radiologist work load only is highlighted. The ability to train existing staff or recruit new staff to undertake this work will also impact on any change in service delivery, given existing issues with pathology staff recruitment and retention. This needs consideration also.	The section has been amended to mention the expected impact to other pathology staff (including BMS and pathologists). Some changes in training are expected and could require additional NHS resource use in the short term, but CNB was found to be cost-effective in the economic analysis and its use after Thy1 and Thy3a is expected to offset initial costs.
Royal College of Radiologists (RCR)	Guideline	009	013 -015	Rec 1.3.2- it should be acknowledged that there is an ongoing NIHR funded trial (HoT) addressing this question and that there is uncertainty regarding the benefits of hemithyroidectomy vs total thyroidectomy. I am surprised that this is not included in the recommendations for further research as this is a key question in the management of low risk thyroid cancer	Thank you for your comment. This is acknowledged in the committee discussion of evidence report H. We will make the NICE surveillance team aware of the study. The committee did not write a research recommendation for hemi-thyroidectomy versus total thyroidectomy because they were aware that the HOT trial addresses this comparison. Instead, they focused on a research recommendation for active surveillance versus surgery.
Royal College of Radiologists (RCR)	Guideline	010	001 - 003	Rec 1.3.4- again, patients in this category should be offered participation in the HoT trial where this is available as there is uncertainty as to the value of completion thyroidectomy in this group.	Thank you for your comment. Recommending people for inclusion in the HOT trial is beyond the scope of this guideline. The trial web page (https://www.isrctn.com/ISRCTN17004671) lists the participating centres. It is anticipated that anyone attending these centres may be considered for inclusion in the HOT Trial if they meet the inclusion criteria.

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Royal College of Radiologists (RCR)	Guideline	011	009 -012	Rec 1.3.12- it is disappointing that a stronger recommendation than 'consider' cannot be made for the majority of patients to receive thyrotropin alfa. I appreciate that this is a cost effectiveness issue, but I am not convinced that the cost effectiveness analyses undertaken have truly taken into consideration all costs associated with THW. Assumptions are made about 0-50% patients being converted to T3, whereas the vast majority of UK centres would convert 100% to T3 if using THW, incurring significant costs. There is also the risk of considerable wastage and inefficiency if TSH levels are not adequately elevated on the day of treatment- it is not just a simple as giving thyrotropin alfa on the day- it is likely that treatment would have to be completely rebooked and that dose of iodine wasted, creating a radiation protection hazard and need to store radioactive material until it has decayed. The more rapid clearance of RAI following thyrotropin alfa also opens up the possibility of day case treatment for low-activity ablations, again achieving significant cost savings compared with an inpatient stay. There are also wider costs to the patient from additional time off work, and potentially for other family members having to provide childcare for longer due to slower clearance of RAI after THW. It is very difficult to quantify all of these additional costs, but they are very significant for a significant number of our patients.	Thank you for your comment. After a further discussion with the committee and to avoid a potentially harmful disruption of current practice, the guideline has been changed to recommend that all people who are having radioactive iodine (RAI) should also receive pretherapeutic stimulation with thyrotropin alfa (recommendation 1.3.12). Several scenarios were tested regarding T3 and showed to the committee, including a scenario where all the patients switched to T3 before the treatment. The results of this scenario have been added to the tables in the evidence and economic reports: cost per QALY = £23,000. The impact of T3 is expected to decrease in the future following the ongoing downward trend started in 2018 that brought the price of the drug down to 1/4 its original price in 2018. The model inputs on adherence in the base case scenario are in line with the evidence from the trials that did not find differences in TSH levels between the two groups. However, as we were concerned these may not be reflecting real world outcomes, consequences of lack of adherence were explored in the threshold analysis. This found that even small decreases of adherence would have a high impact on the conclusion of the analysis. If TSH level

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

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Stakeholder	Document	Page No	Line No	Comments	Developer's response
					is expected to be routinely insufficient with withdrawal, withdrawal is unlikely to be cost-effective. Differences in clearance duration of RAI were explicitly considered in the model in terms of hospital length of stay (LOS) as this directly affects NHS spending. Although only ESTIMBAL reported this outcome explicitly (0.2) an extrapolation based on HiLo (UK) found a similar number (0.1). The higher value from ESTIMABL was ultimately used in the model as it could be directly taken from the study and did not require approximation or extrapolation (unlike HiLo). Time off work and equality considerations could not be incorporated into the economic model but were widely discussed by the committee. They are reported in the rationale and committee discussion of evidence report I and are part of the reason the committee changed the recommendation to a stronger 'offer' recommendation.
Royal College of Radiologists (RCR)	Guideline	012	006 - 008	Rec 1.3.17- This recommendation does not acknowledge the recent findings of the ESTIMABL 2 trial [Leboulleux S et al. Thyroidectomy without radioiodine in patients in low-risk thyroid cancer. NEJM 2022; 386:923-32]. I appreciate that this was published after the cut off date for the literature search for this guideline, but this is really important data which is already impacting practice in the UK and if not included the guideline risks being out of date before it is	Thank you for your comment. ESTIMABL2 trial has been added to the guideline review. Based on this evidence the committee have updated the recommendation to 'Do not offer RAI to people with T1a or T1b tumours including those with multifocal disease, unless there are adverse features or evidence of metastatic disease**'.**

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

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Stakeholder	Document	Page No	Line No	Comments	Developer's response
				published. Essentially this study shows that for patients with up to T1bN0 disease without adverse histological factors RAI is not of benefit. If should perhaps also be acknowledged that results of the UK IoN trial are awaited and these will potentially further significantly change which groups we recommend RAI for.	Evidence report J has been updated with the new evidence and the committee's interpretation of the evidence is contained in the committee discussion section.
Royal College of Radiologists (RCR)	Guideline	013	002	It would be helpful to start the section on external beam radiotherapy with a statement that there is not a routine role for external beam radiotherapy in the adjuvant treatment of thyroid cancer to make it clear that the subsequent guidance relates only to a very small subgroup of patients.	Thank you for your comment. We have added this to the start of the rationale, which will appear immediately below the recommendations.
Royal College of Radiologists (RCR)	Guideline	013	003 - 004	Clarification should be made here that in most cases RAI should be given before EBRT- so perhaps modifying Rec 1.3.20 to 'Consider external beam radiotherapy ***after RAI*** if there is macroscopic disease after 3 surgery or local disease that is unlikely to be controlled with RAI.'	Thank you for your comment. We didn't consider the sequencing of EBRT and RAI and therefore have not made recommendations in this area. The committee also did not want to specify the sequencing of RAI and EBRT. The agreed that while giving EBRT after RAI may be the norm there may be circumstances that a clinician would decide to offer EBRT before RAI.
Royal College of Radiologists (RCR)	Guideline	014	002 - 003	Rec 1.4.3- the technical term for patient who 'respond well to initial treatment' in the dynamic risk stratification scheme is 'excellent response'. It would be more helpful if this term was used here.	Thank you for your comment. The committee agree and we have updated the recommendation to 'Reduce TSH suppression to achieve a TSH level of between 0.3 mIU/litre and 2.0 mIU/litre and continue this for life in people with excellent responses to treatment'.

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

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Stakeholder	Document	Page No	Line No	Comments	Developer's response
Royal College of Radiologists (RCR)	Guideline	014	011 -013	Rec 1.4.5- whilst I agree that TSH suppression should be reviewed after 10 years, I think some comment needs to be made here that if a decision is made to relax suppression this needs to be done carefully and with support and regular review as a proportion of patients will experience a deterioration in quality of life and significant symptom problems when thyroxine doses are reduced.	Thank you for your comment. The committee agree and think this is a good idea. The recommendation has been updated to state: Offer a review to people who have had ongoing TSH suppression for more than 10 years. Decide whether the TSH suppression can be reduced after an individualised assessment of risks and benefits, and explain that: • lifelong suppression is not necessary unless they have high-risk or metastatic disease • avoiding complete TSH suppression may reduce the risk of developing bone and cardiac problems
Royal College of Radiologists (RCR)	Guideline	017	004 - 007	Rec 1.6.2- it should be clarified here what is meant by 'annual follow up'. Currently it is not clear whether this means annual ultrasound, or simply clinical follow up. If annual ultrasound is being recommended this has significant resource implications as this is not currently being undertaken in most centres.	Thank you for your comment. The committee agreed there wasn't clear evidence on when and if ultrasound should be used after the initial follow up ultrasound. Therefore, they left it for the clinician to decide whether to do ultrasound at follow up reviews. We have added this to the rationale and updated the recommendation to state it is annual clinical follow up.
Royal College of Radiologists (RCR)	Guideline	017	010 -011	Rec 1.6.3- similarly in this table, it would be helpful to clarify advice regarding the frequency of ultrasound follow up- in most centres if all is well at initial dynamic risk stratification this will not be repeated unless new symptoms or change in thyroglobulin. Advocating routine ultrasound follow up will have very significant resource implications	Thank you for your comment. We have updated table 2 and the rationale to make it clearer that ultrasound is only recommended on a case by case basis. The clinician would assess whether it is needed.

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Royal College of Radiologists (RCR)	Guideline	021	003 - 005	Research recommendations- radioactive iodine. Further research is recommended regarding clinical and cost effectiveness of RAI for tumours ***at stages 2b or 3.*** I do not recognise these as thyroid tumour stages within TNM 8. Please clarify which tumour stages are being referred to here, ideally using TNM classification.	Thank you for your comment. We have updated the research recommendation and, following on from stakeholder comments, we have also limited the research recommendation to T2 disease.
Royal College of Radiologists (RCR)	Guideline	029	020 -024	It is not technically true that molecular tests are unavailable in the UK. The Genomics England Test Directory includes the possibility of testing for BRAF, KRAS, NRAS, HRAS, TERT, RET and NTRK alterations to aid the diagnosis and management of thyroid cancers. I agree that further research is required in this area, but this statement should be adjusted to ensure it is factually accurate.	Thank you for your comment. We have changed this to '..molecular tests are not widely available in the NHS…'
Royal College of Speech and Language Therapists	Guideline	003	018 - 019	RCSLT welcomes acknowledgement of the importance of ensuring patients are well informed and prepared for treatment. RCSLT would expect risk of voice change and swallowing disorders to be included in discussion of potential implications of surgery. **See:** Pitt SC, Wendt E, Saucke MC, Voils CI, Orne J, Macdonald CL, Connor NP, Sippel RS. A Qualitative Analysis of the Preoperative Needs of Patients With Papillary Thyroid Cancer. J Surg Res. 2019 Dec;244:324-331. doi: 10.1016/j.jss.2019.06.072. Epub 2019 Jul 12. PMID: 31306889; PMCID: PMC6815701.	Thank you for your comment. The committee agree and have added the potential for voice change and swallowing disorders as a separate bullet point to the recommendation 1.1.4 on information for people having surgery.

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

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Stakeholder	Document	Page No	Line No	Comments	Developer's response
Royal College of Speech and Language Therapists	Guideline	General	General	The guideline states on p47 the potential risk of vocal fold palsy but does not address actions that could be taken to support patients who end up with this complication. By comparison, for example, the hormonal medication as a treatment for those patients without a thyroid is referenced (also pg.47). Voice and swallowing problems are common after thyroid surgery, and research has found this is not only in instances where there is injury to the recurrent laryngeal nerve. RCSLT recommends that these guidelines should include: a) an acknowledgement of the risks of voice change and swallowing disorders from thyroid surgery. b) a recommendation that patients' voice and swallow should be assessed before and after thyroid surgery, in order to identify changes. c) a recommendation that, where patients experience vocal fold palsy, voice or swallowing changes, there should be liaison with Ear, Nose and Throat and/or speech and language therapy services regarding further assessment and possible treatment. **Please see references for the above:**	Thank you for your comment. A bullet point has been added to recommendation 1.1.4 so that this now includes providing people with having surgery information on the 'potential for voice change and swallowing disorders'. Assessment of the person's voice and swallowing before surgery, and liaison with Ear Nose and Throat and/or speech and language therapy services were not included as part of the scope. Therefore, the committee are unable to make recommendations in this area.

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Chandrasekhar SS, Randolph GW, Seidman MD, Rosenfeld RM, Angelos P, Barkmeier-Kraemer J, Benninger MS, Blumin JH, Dennis G, Hanks J, Haymart MR, Kloos RT, Seals B, Schreibstein JM, Thomas MA, Waddington C, Warren B, Robertson PJ; American Academy of Otolaryngology-Head and Neck Surgery. Clinical practice guideline: improving voice outcomes after thyroid surgery. Otolaryngol Head Neck Surg. 2013 Jun;148(6 Suppl):S1-37. doi: 10.1177/0194599813487301. PMID: 23733893. Gregorio Scerrino, Chiara Tudisca, Sebastiano Bonventre, Cristina Raspanti, Dario Picone, Calogero Porrello, Nunzia Cinzia Paladino, Federica Vernuccio, Francesco Cupido, Gianfranco Cocorullo, Giuseppe Lo Re, Gaspare Gulotta, Swallowing disorders after thyroidectomy: What we know and where we are. A systematic review, International Journal of Surgery, Volume 41, Supplement 1,2017, Pages S94-S102, ISSN 1743-9191, https://doi.org/10.1016/j.ijsu.2017.03.078. Henry LR, Helou LB, Solomon NP, Howard RS, Gurevich-Uvena J, Coppit G, Stojadinovic A. Functional voice outcomes after thyroidectomy: an assessment of the Dsyphonia Severity Index (DSI) after thyroidectomy. Surgery. 2010 Jun;147(6):861-70.	

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				doi: 10.1016/j.surg.2009.11.017. Epub 2010 Jan 21. PMID: 20096434. Ryu et al Care and Management of Voice Change in Thyroid Surgery: Korean Society of Laryngology, Phoniatrics and Logopedics Clinical Practice Guideline. Clin Exp Otorhinolaryngol. 2022;15 (1): 24-48. Publication Date (Web): 2021 June 01 (Guideline) doi:https://doi.org/10.21053/ceo.2021.00633 Tufan Gumus, Ozer Makay, Sibel Eyigor, Kerem Ozturk, Zeynep Erdogan Cetin, Baha Sezgin, Zeynep Kolcak, Gokhan Icoz, Mahir Akyildiz, Objective analysis of swallowing and functional voice outcomes after thyroidectomy: A prospective cohort study, Asian Journal of Surgery, Volume 43, Issue 1, 2020, Pages 116-123, ISSN 1015-9584, https://doi.org/10.1016/j.asjsur.2019.04.013.	
Royal College of Surgeons of Edinburgh	Guideline	007	014	Rec 1.2.9 - The recommendation for use of an ultrasound staging system if very welcome. There are currently 2 broad categories of systems used in the UK. Those bases on an interpretation of the nodule against certain specific criteria (i.e., U and EU TI RADS) and those using a direct binary scoring system looking at specific criteria and given an ultimate score (ACR TI RADS). Both systems have been validated but the former is very much more open to operator	Thank you for your comment. Following stakeholder comments the committee agree that the recommendation referring to EU-TIRADS is unhelpful and have removed it from the guideline. The original recommendation was made because the committee believed EU-TIRADS showed the most promising results. However, the committee agree that without evidence to recommend a whole system this gives too much emphasis to EU-TIRADS and may make it

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

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Stakeholder	Document	Page No	Line No	Comments	Developer's response
				dependence with most of the work having been done in specialist centres. In order to be applicable, we need data on the real-world applicability of these systems and in this case the Scoring system as used in the ACR TI RADS is likely to be more reproducible in the non-specialist setting. The ACR TIRADS also enables surveillance of nodules within its algorithm or even discharging patients below certain size thresholds that is very useful and avoids over investigation. The omission of any mention of ACT TIRADS within this document means effectively it will be difficult to continue using it (and the advantages it brings with it) in the UK. Given that at present time there is such a variation in practice in the UK from some being scored but still a significant number not being scored at all would it not be better to recommend that anyone of the scoring systems be used and the threshold for FNAC be based on that scoring system (the current recommendation seems to be some kind of hybrid) The diagnosis of papillary thyroid cancer is generally not particularly contentious, the difficulties in diagnosis arise in those patients with Follicular lesions i.e. the U3/ ACT TIRADS 3 and EU TIRADS 3 This has not been addressed.	difficult to use or continue to use alternative systems such as BTA guidelines or ACR TIRADS. The guideline no longer highlights any particular scoring system. There is still a cross reference to the NICE guideline on thyroid disease (https://www.nice.org.uk/guidance/ng145) which recommends 'When making decisions about whether to offer fine needle aspiration cytology, use an established system for grading ultrasound appearance'. A review of the evidence on size for tumour was included as part of the guideline. As no evidence was found that met the protocol no recommendations were made in this area. The protocol and details of this review are included as part of evidence report A.

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				There is no mention of a size cut-off for FNAC (Current practice in UK is 10mm but in EU—TIRADS they would normal only sample >15mm if score is 4 but would also sample a sore of 3 if > 20 mm) in practice if this is followed, we are going to sample a lot more nodules and subject patients to significantly more potential morbidity in terms of both surgery and anxiety. The biggest issue in managing papillary Thyroid cancer is not its early diagnosis but its over investigation, over investigation and overly aggressive management. The recommendation of doing an FNAC on EVERY TR4 and TR5 Lesion with no size criteria for either discharge or follow up will lead to this with patients being operated on for clinically insignificant nodules that would never lead to clinically relent disease.	
Royal College of Surgeons of Edinburgh	Guideline	010	014	1.3.9 - Need to clarify that this is only in relation to papillary and follicular thyroid cancer not medullary	Thank you for your comment. We have made the section titles in the guideline clearer to emphasise that the recommendations for treatment only relate to differentiated thyroid cancer.
Royal College of Surgeons of Edinburgh	Guideline	010	017	1.3.10 - Maybe include or until second trimester in high-risk malignancies i.e with evidence of nodal metastasis or rapid growth	Thank you for your comment. The committee agree your point and have added another recommendation in line with your comment. This states '1.3.11 When surgery cannot be delayed until after pregnancy, it should be done during the second trimester if possible.'
Royal College of	Guideline	010	020	Should we not be advocating this as the standard of care given the significant impact of Thyroid Hormone	Thank you for your comment. After a further discussion with the committee and to avoid a

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Surgeons of Edinburgh				Withdrawal on our patients of all ages not just those working?	potentially harmful disruption of current practice, the guideline has been changed to recommend that all people who are having radioactive iodine (RAI) should also receive pretherapeutic stimulation with thyrotropin alfa (recommendation 1.3.12).
Royal College of Surgeons of Edinburgh	Guideline	015	014	1.5.3 – need to clarify what is meant by a positive thyroglobulin test; is it one that is showing an increasing trend as the absolute number can vary	Thank you for your comment. We have updated the wording so that instead of 'positive thyroglobulin levels' we state 'detectable thyroglobulin levels', and instead of 'negative thyroglobulin antibodies' we state 'without thyroglobulin antibodies'.
Royal College of Surgeons of Edinburgh	Guideline	017, 045	004, 021	These 2 statements are not the same (the first is the Guidance) while ultrasound follow up is implied it is not clear and follow up could mean clinical the clarification on page 45 is more forthcoming on this. While this seems sensible for those that have had a hemi thyroidectomy (although you could argue that if no recurrence at 1 year every 2 years would be reasonable). For those that have had a total thyroidectomy this does not seem to be considering the Thyroglobulin level. If this was undetectable or low and stable, then does an annual USS for 5 years really make sense? Why not annual TG	Thank you for your comment. The committee agreed there wasn't clear evidence on when and if ultrasound should be used after the initial follow up ultrasound. Therefore, they left it for the clinician to decide whether to do ultrasound at follow up reviews. We have added this to the rationale and updated the recommendation to state it is annual clinical follow up. They also agreed that there may occasionally be instances when it is appropriate to measure thyroglobulin in people who had a total thyroidectomy but not had RAI. They agreed that detectable thyroglobulin alone does not indicate recurrence of cancer. This has been added to the rationale.
Society for Endocrinology	Guideline	003	009	Rec 1.1.2: most lumps, nodules or swellings in the thyroid are NOT cancer – this needs rewording	Thank you for your comment. While the committee agree that most lumps are not cancer they think the wording as originally written is better. They have concern that using the wording you suggest changes

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					the emphasis and could send out the wrong message to less experienced clinicians. If there is a lump in the neck it needs investigating.
Society for Endocrinology	Guideline	003	018	Rec 1.1.4: risks – these need to be specified since presumably these are not the risks of hypothyroidism and hypoparathyroidism which are discussed in different bullet points	Thank you for your comment. The recommendation (1.1.4) has been amended so that the stem mentions the risk and benefits and the bullet points just list the key long-term implications.
Society for Endocrinology	Guideline	003 - 004	020 - 021	Rec 1.1.4These bullet points should be joined up as they are related to the same complication i.e. hypothyroidism	Thank you for your comment. The committee agree and have merged the two bullet points in the recommendation. The bullet point now states 'hypothyroidism and the subsequent need for lifelong thyroid hormone replacement'
Society for Endocrinology	Guideline	006	012 - 015	Recs 1.2.8 and 1.2.9: it is unclear why the threshold for FNAC is only stated for one of the scoring systems. Many centres in the UK use a U scoring system and the threshold for FNA is not given for this. The guideline leaves the use of particular scoring systems open to individual practitioners and centres which is fine but it seems wrong to then give specific advice on just one scoring system – EU TIRADS	Thank you for your comment. Following stakeholder comments the committee agree that the recommendation referring to EU-TIRADS is unhelpful and have removed it from the guideline. The guideline no longer highlights any particular scoring system. There is still a cross reference to the NICE guideline on thyroid disease (https://www.nice.org.uk/guidance/ng145) which recommends 'When making decisions about whether to offer fine needle aspiration cytology, use an established system for grading ultrasound appearance'.
Society for Endocrinology	Guideline	006	016 -018	Rec 1.2.10 I find it difficult to envisage in which situation diagnostic hemithyroidectomy would be done based on US findings alone. I can see why FNAC and active surveillance may be suitable approaches if there	Thank you for your comment. The committee agree and have removed diagnostic hemithyroidectomy as an option. They agreed that the reasons for doing a diagnostic hemithyroidectomy would not relate to the cancer, rather it would relate to problems associated

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				are concerns about nodules with and ultrasonographic scoring that does not reach the threshold for FNAC	with non-malignant thyroid disease such as compression. The benefits and harms section of evidence report A has been updated to reflect this.
Society for Endocrinology	Guideline	009	017 -018	Rec 1.3.10 I suggest surgery is delayed until AFTER pregnancy. Surgery in the 3rd trimester – at the end of pregnancy is associated with significant risks to fetus and mother	Thank you for your comment. The committee agree with your suggestion and have updated the recommendation to 'until after pregnancy'.
Society for Endocrinology	Guideline	013	017 -018	Rec 1.4.2 I suggest that TSH suppression should be continued until dynamic risk stratification is undertaken. Not a blanket 1 year for all	Thank you for your comment. The committee agree and have amended the recommendation to state '…TSH suppression should be continued until follow up review at 9 to 12 months after initial treatment has been completed.'. This makes it consistent with the following recommendation 1.4.3 which recommends using dynamic risk stratification to determine further management. This includes advising when TSH suppression can be reduced.
Society for Endocrinology	Guideline	014	004 - 006	Rec 1.4.6: do you mean a TSH concentration BETWEEN 0.1 and 0.5 mIU/L? In clinical practice this is nearly impossible to achieve! Although it is what is recommended by most guidelines	Thank you for your comment. Yes, this should have stated 'between 0.1 and 0.5mIU/L' and has been corrected. However, the committee do not agree that this is nearly impossible to achieve.
Society for Endocrinology	Guideline	014 - 015	001 -017	Recs 1.5.1, 1.5.2 and 1.5.3 I find the terminology of positive and negative thyroglobulin test and positive thyroglobulin levels confusing. The terminology is not consistent and rising thyroglobulin levels is also used. This needs be more clear. Do you mean thyroglobulin levels raised above the upper limit of normal – better even some indication of how high a raised thyroglobulin has to be to be considered significant.	Thank you for your comment. We have updated the wording so that instead of 'positive thyroglobulin levels' we state 'detectable thyroglobulin levels', and instead of 'negative thyroglobulin antibodies' we state 'without thyroglobulin antibodies'. The committee agree there may be times when mildly raised thyroglobulin levels may not represent residual

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Mildly raised Tg levels often are not necessary recurrent or residual disease. Of note some Tg concentrations are used in the other recs in 1.5	and recurrent disease but it is difficult to define these circumstances. They have made a softer 'consider' recommendation to reflect there is some uncertainty in the recommendations.
Society for Endocrinology	Guideline	017	004 - 007	Rec 1.6.2: do you mean annual FU with ultrasound? Or clinical follow-up. That would be a huge number of ultrasounds if annually in people with low risk thyroid cancer! The table below is more nuanced and better and I think this recommendation should refer to the risk stratified approach	Thank you for your comment. The committee agreed there wasn't clear evidence on when and if ultrasound should be used after the initial follow up ultrasound. Therefore, they left it for the clinician to decide whether to do ultrasound at follow up reviews. We have added this to the rationale and updated the recommendation to state it is annual clinical follow up.
Society for Endocrinology	Guideline	017	013 - 014	Rec 1.6.4 I think this should be worded as MDT discussion and consideration of surgery. This rec seems to be worded a little clumsily.	Thank you for your comment. We have updated the recommendation to state '1.6.4 "Discuss at the multidisciplinary team meeting if the person has had a total or completion thyroidectomy and RAI and has evidence of structural persistent disease"
Society for Endocrinology	Guideline	General	General	The title of the guideline needs to make clear that the guideline relates to differentiated thyroid cancer and not medullary, anaplastic and other cancers	Thank you for your comment. The guideline relates to the diagnosis of all thyroid cancer and treatment of differentiated thyroid cancer. To make this clearer we have labelled the section titles related to treatment as 'differentiated thyroid cancer'.
Society for Endocrinology	Guideline	General	General	The introductory box needs to clarify that the guideline and recommendations relate to the diagnosis and management of differentiated thyroid cancer	Thank you for your comment. The guideline relates to the diagnosis of all thyroid cancer and treatment of differentiated thyroid cancer. To make this clearer the introductory paragraph has been updated as suggested.
Society for Endocrinology	Guideline	General	General	Throughout the document there is no mention of MDT. MDT discussions are crucial in the management of these patients and this seems remiss. Indeed most	Thank you for your comment. The guideline focuses on which interventions to recommend rather than issues around service delivery. There is an

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				MDTs will have to revise some of their protocols based on the guidelines	assumption that MDTs will happen as they are current practice. Two recommendations have been updated to mention them: 1.1.8 on patient information and 1.6.4 on follow up.
The Thyroid Trust	Guideline	004	003	Rec 1.1.4 Given the high risk of hypoparathyroidism/hypocalcaemia we would recommend strengthening this to read 'Potential need for treatment of either temporary or permanent post-operative low calcium and parathyroid hormone and its short- and long-term consequences' (including removal of the word 'possible')	Thank you for your comment. The word 'possible' has been removed and the recommendation updated to state 'the potential for and possible consequences of the need for treatment for low parathyroid hormone'. The committee think the rest of the point as written is clear and concise and prefer to keep the recommendation this way.
The Thyroid Trust	Guideline	004	003	Rec: 1.1.6 We are happy to see that the guideline strongly advises against using the term 'the good cancer'	Thank you for your comment and support for the recommendation.
The Thyroid Trust	Guideline	004	026	Rec 1.1.8 line 26 we are concerned that this sentence is too vague and would prefer to see it amended to 'Give the names and roles of those who will be involved in their treatment and follow-up including the composition of the MDT'	Thank you for your comment. Recommendation 1.1.8 has been amended to 'the roles of those involved in their treatment and follow up, and the composition of the multidisciplinary team'. The names of those involved was not included as these might change and it is recommended that people are told who their key worker is and who to contact for more information.
The Thyroid Trust	Guideline	005	015	Rec 1.2.2 We are concerned that restricting calcitonin testing to those individuals with a family history of medullary thyroid cancer (MTC) or a nodule that is suspicious for MTC, is too blunt an instrument, as there is a risk albeit small of missing cases of MTC at an early stage. There appears to be no clear	Thank you for your comment. The recommendation was based on the lack of evidence and current assay costs. The committee agreed that the high cost and the rare prevalence of medullary cancers (around 100-150 of new cases per year in the UK) makes its

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				consensus in the current American and European guidelines and we therefore propose that this subject is kept under review. See Verbeek et al. Calcitonin testing for detection of medullary thyroid cancer in people with thyroid nodules. (2020) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7075519/	routine use unlikely to be cost effective unless there is a suspicion of medullary thyroid cancer.
The Thyroid Trust	Guideline	011	017	Rec 1.3.13 We are encouraged to note that the Guideline mentions that people who undergo thyroid hormone withdrawal (THW) may need to take 2-3 weeks off work following RAI treatment	Thank you for your comment. After a further discussion with the committee and to avoid a potentially harmful disruption of current practice, the guideline has been changed to recommend that all people who are having radioactive iodine (RAI) should also receive pretherapeutic stimulation with thyrotropin alfa (recommendation 1.3.12). Considerations on the impact of THW on time off work are now included in the committee discussion of evidence report I and explained in the rationale.
The Thyroid Trust	Guideline	011	017	Rec 1.3.13 It would be useful to add that at least one study has found that patients suffer marked cognitive impairment and should not be driving during THW, see Smith et al Reversible cognitive, motor, and driving impairments in severe hypothyroidism (2015).	Thank you for your comment. After a further discussion with the committee and to avoid a potentially harmful disruption of current practice, the guideline has been updated to recommend that all people who are having radioactive iodine (RAI) should also receive pretherapeutic stimulation with thyrotropin alfa. We have not included a comment about the impact on driving as we did not consider this as part of the review and the manufacturers patient information

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					leaflet already cautions about driving when on thyrotropin alfa.
The Thyroid Trust	Guideline	012	004	Rec 1.3.16 We recommend including an explanation of 'adverse features'	Thank you for your comment. The committee have updated the recommendation to 'Do not offer RAI to people with T1a or T1b tumours including those with multifocal disease unless there are adverse features or evidence of metastatic disease'. Multifocality was an adverse feature included in ESTIMABL2 that did not affect the outcome. The committee agreed that other adverse features are quite varied and the clinician would need to make a judgement on a case by case basis. The benefits and harms section of the committee discussion in evidence report J has also been updated.
The Thyroid Trust	Guideline	012	010	Rec RAI activity - It is disappointing to note that there is no mention of short- and potential long-term side effects of RAI including salivary gland disease which we feel should be noted here	Thank you for your comment. The committee did not consider this as an outcome in the review. They agreed it is far less common than it was previously and less of a risk with modern practice. However, they do agree that some mention of the risks of RAI should be made in the guideline including mention of salivary glands. We have added another recommendation on information for people having radioactive iodine' in section 1.1 'Information and support'. This recommends offering people written and verbal information on the short and long term risks of radioactive iodine and includes the bullet point: 'Although uncommon there is the potential for dry mouth and salivary gland inflammation both of which are temporary in most people'

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
The Thyroid Trust	Guideline	016	001	1.6 Follow-up – It should be noted that 'Once a thyroid cancer patient, always a thyroid cancer patient'. Although most patients survive and thrive, thyroid cancer is a life-long chronic condition and in rare cases can recur and/or develop as radioactive iodine resistant thyroid cancer. Patients increasingly move around the country or overseas and we have noted several instances among our members who found it difficult to get hold of their notes and advice how to get follow-up after moving including one instance where a patient initially classified as low risk had a recurrence 20 years after the first occurrence while living in a foreign country. It would be helpful to remind physicians of the importance of providing patients with clear (preferably written) advice about long term follow-up and how to access information when moving within the UK or when moving to another country.	Thank you for your comment. The committee agree that the transfer of records is an important issue. They also noted that it is part of a wider issue that covers a range of conditions. They have not made recommendations in this area as it was not included as part of the scope for this guideline.
UK Endocrine Pathology Society	Evidence review D	005	008 - 024	1.1.2 and later The guideline states that '*Core biopsy follows the RCPath FNAC classification system'* **This statement is misleading and needs rewording.** The RCPath Tissue Pathways for Endocrine Pathology published in 2019 states in the last paragraph of page 9 that ***'It may be helpful to categorise core biopsies in a manner similar to those used for thyroid cytology'*** **but RCPath does not specifically state how to report CNB of the thyroid** so the statement above is not accurate.	Thank you for your comment. The committee agree and we have deleted this statement from the introduction of evidence review D.

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				There is no agreed international or UK reporting terminology system for reporting needle core biopsies of the thyroid gland because the inherent problems of thyroid needle core biopsy interpretation. There is a Korean NCB reporting terminology system, (see Na DG et al. Korean J Radiol 2017;18:217-237) but it is not used in the UK as it has multiple indeterminate categories with low levels of inter-observer agreement and reproducibility. Microsoft Word - G078 Tissue pathways for endocrine pathology For Publication.docx (rcpath.org)	
UK Endocrine Pathology Society	Evidence review D	005	002	1.1.3 and throughout whole document The review question is... 'For people with thyroid nodules that require further investigation following ultrasound, what is the diagnostic accuracy of fine needle aspiration cytology (FNAC) with rapid on-site assessment, FNAC without rapid on-site assessment or core biopsy for diagnosing thyroid cancer. The guideline states 'consider using cytospin and cell block in addition to, or instead of smear when processing FNAC samples.' This statement is based on an extensive review of the literature in Evidence Review D. The cases are PIRO classified as follows FNAC without rapid on-site assessment (ROSA) with smear without cytospin and cellblock FNAC without ROSA with Cytospin and cell block, without smear.	Thank you for your comment. We have updated the wording in the recommendation, rationale and committee discussion in evidence review D to 'liquid based cytology' in response to your comment in the last paragraph on proprietary trademarks. The committee agreed that 'liquid based cytology' is a generic term that includes 'Cytospin and cell block' and is therefore more appropriate to use in a guideline recommendation.

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				FNAC without ROSA with smear, cytospin and cell block FNAC with ROSA (by cytopathologist or technician) and with smear without cytospin and cell block FNAC) with ROSA (by cytopathologist or technician) and with smear with cytospin and cell block Core biopsy As 'Cytospin' is a trademark and is one of several cytocentrifuge techniques the wording throughout this document in the text where the term cytospin is referred to should be changed to. FNAC without rapid on-site assessment (ROSA) with smear without cytocentrifuge technique and cellblock FNAC without ROSA with cytocentrifuge technique and cell block, without smear. FNAC without ROSA with smear, cytocentrifuge technique and cell block FNAC with ROSA (by cytopathologist or technician) and with smear without cytocentrifuge technique and cell block FNAC) with ROSA (by cytopathologist or technician) and with smear with cytocentrifuge technique and cell block Core biopsy	

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
UK Endocrine Pathology Society	Evidence review D	005	002	1.1.3 and throughout whole document Several of the articles cited in this section refer to cytocentrifuge techniques (referred to as cytospin) being used in addition to conventional FNAC. Some of the articles in Evidence review D describe specimens in which cell blocks are prepared, either via needle washings, or cytocentrifugation of a thyroid cyst fluid, and a much smaller number refer to cases where cytocentrifuge specimens are made, without conventional direct smears. UKEPS would comment as follows (v) Making a cytocentrifuge specimen without examining a direct smear is not performed in most laboratories, because direct smears are needed for diagnosis to readily identify thyroid colloid, which is a benign and clinically re-assuring feature. (vi) If the whole specimen is processed for a cytocentrifuge preparation as the draft guideline suggests when is says '*consider using cytospin and cell block in addition to, or instead of smear when processing FNAC samples'* colloid is either lost or is more difficult to see. (vii) The evidence-based review D examines the rates of the various FNA diagnostic categories; Bethesda I-VI, Thy1-Thy5 etc.	Thank you for your comment. The committee agreed there is huge variation in practice across centres in the UK. Some of the large thyroid centres in the UK have discontinued preparation of direct smears and only use liquid based cytology for more than 10 years without any negative impact on diagnosis. Colloid can also be visualised on well prepared liquid based cytology. The latter also offers excellent cell preservation and suitable material for ancillary testing. The committee, therefore, recommends either technique can be used. The committee agreed that it would be difficult to determine malignancy in people who did not have surgery. Therefore, they agreed that the gold standard to use when assessing evidence for diagnostic accuracy was surgical histopathological findings. They also noted that this is how diagnostic accuracy would be assessed in the evidence. There would be people in these studies with benign tumours who would be reported as false positives. Therefore, while not perfect the committee agreed that the evidence does provide evidence on diagnostic accuracy and the subsequent recommendations are based on the best available evidence.

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				in patients who undergo surgery alone but it does not assess the rates of malignancy in patients who have not undergone surgical excision. **(viii)** Evidence-based review D does not show robust evidence of the diagnostic accuracy of thyroid FNA for assessing benign lesions of the thyroid that have not undergone surgery as patients not undergoing surgery were excluded from the analyses. This is important because the recommendation to use cytocentrifuge techniques appears based on a relatively small number of publications whereas in day to day practice the guideline recommendations will then be applied to all thyroid FNAC. The efficacy of the FNA technique in this guideline is being assessed in relation to the diagnosis of potential cancer, not in the assessment of whether or not a given thyroid nodule is benign, as benign nodules do not undergo surgery. • **The UKEPS as a society notes that the established practice in most UK centres is to make cytocentrifuge preparations for those thyroid FNA's where there is a cyst fluid, or where there is sufficient cellular**	

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				material remaining after making direct smears so that a cell block can be made if needed, although frequently there is insufficient material to make or to attempt to make a cell block when there is a cyst fluid. • **The UKEPS very much disagrees that cytospin preparations should be made in preference to or as a replacement for direct smears, because of the problem of visualising colloid in cytocentrifuge preparations for the diagnosis of benign thyroid lesions.** • **The preferred method would be that direct smears (both air dried and fixed) should be made to assess colloid and cellularity, with a liquid based cytology specimen from any needle washings if available and then a cell block only if there is any cytological material remaining after making direct smears and a liquid based cytology preparation. Cytocentrifuge/cytospin preparations and/ or cell blocks should only be made if needed for diagnosis following direct smear evaluation.**	

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
UK Endocrine Pathology Society	Evidence review D	007	General	1.1.5.1 Why is Bethesda grading being used to capture evidence when the UK uses RCPath reporting terminology ?	Thank you for your comment. We included any data that used any established FNAC classification system. A variety of different systems were used in the included studies and these were meta-analysed according to the system used. Much of the evidence in the review is based on the Bethesda grading scheme which is why this is mentioned so frequently within the committee discussion of the evidence report. We also noted here that the Bethesda classification scheme is not commonly used in the UK. Therefore, the committee recommended that a Bethesda-equivalent scheme widely used in the UK called the RC PATH modification of the BTA (RC PATH BTA) should be used instead. The committee agreed that this uses qualitatively similar grades, whilst the main difference is fairly superficial, based on the labelling of each grade. RC PATH BTA grades Thy 1, 2, 3a, 3f, 4 and 5 are equivalent to Bethesda grades I, II, III, IV, V and VI respectively. We have added reference to the revised RCPath to table 3 of evidence report D.
UK Endocrine Pathology Society	Evidence review D	007	026 - 027	Line 26-27 'BTA' should read 'RCPath'	Thank you for your comment. We have amended this to revised Royal College of Pathologists (RCPath).

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
UK Endocrine Pathology Society	Evidence review D	007	038	1.1.5.1 Line 38-9. "equivalent to Bethesda grades" - this UK document is rather Bethesda-heavy and could usefully include RCPath Thy classification as well at places such as this	Thank you for your comment. Bethesda is referenced a lot in the guideline because a lot of the evidence related to this system of reporting. We have included reference to the RCPath within the report. We acknowledge in the committee discussion (evidence review D) that much of the evidence in the review is based on the Bethesda grading scheme and that the Bethesda classification scheme is not commonly used in the UK.
UK Endocrine Pathology Society	Evidence review D	008 - 035	General	1.1.5.1, Table 2 Some of the references are very old, 1980s, how relevant are these today?	Thank you for your comment. The committee agreed that old data would still be relevant to this review. All papers were quality assessed to agreed processes. This point has been noted in the quality of evidence section in the committee discussion of evidence report D.
UK Endocrine Pathology Society	Evidence review D	008 - 035	General	1.1.5.1 Table 2 Some UK references appear to have been omitted, eg Newcastle have published a major series of correlation of thyroid FNA with histological findings but Parkinson D et al. J Clin Pathol doi: 10.1136/jclinpath-2016-204022 is not cited in the evidence based review	Thank you for your comment. We have checked this study and it would have been excluded due to type of FNAC not reported within the study.
UK Endocrine Pathology Society	Evidence review D	089 – 091	General	Table 22 "CB grades" in numerical numbers suggesting using Bethesda categories for core biopsies, this is not correct	Thank you for your comment. This is reported with roman numerals as that is how the study reported the results.
UK Endocrine Pathology Society	Evidence Review D	098	002	1.1.13 The economic analysis assumes a scientific band 4. To provide ROSA which is technically demanding if a clinical decision needs to be made in clinic whether to	Thank you for your comment. The analysis has been amended to include the role of a cytopathologist. A recent RCPath survey on

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				repeat the aspirate or perform needle core biopsy or discharge a patient it would require a consultant cytopathologist so the cost of ROSA needs to be revised in this costing. The examination using ROSA also requires a rapid direct smear technique, typically Diff-quick, to be examined in clinic and if necessary, with further direct smears and a cell block/cytocentrifuge if sufficient cytological material remains. **The cost stated of £38 per hour in 1.1.13 would therefore not be sufficient.**	cytopathology practice in the UK found a 50% split between BMS and pathologists among those performing ROSA. The calculation has been amended accordingly finding a cost of ROSA equal to £70, which is in line with other UK estimates.
UK Endocrine Pathology Society	Evidence Review D	098	029	The baseline adequacy rate was derived from an evidence-based review, not a meta-analysis for Thy1 FNA, and this figure excluded cystic lesions Thy1c. The figures are not derived specifically from an RCPath publication, but rather from an evidence-based review that is misquoted. The correct reference is Poller DN et al Cytopathology;2020:31(6)502-508	Thank you for your comment and clarification. The in-text description and references have been amended. We looked at the study and could confirm that this figure does indeed include cystic lesion Thy1c. This figure was calculated from column 6 of table 4 reporting the overall percentage of Thy1. Only 3 studies in column 7 reports the proportion of Thy1c. The proportion of 18.5% was calculated across all studies in column 6 and, therefore, includes cystic lesions Thy1c.
UK Endocrine Pathology Society	Evidence review D	102	028	1.15.4 '*The additional cost of ROSA is estimated to be £28, 44 minutes of the hourly cost of a cytopathologist*.' As stated above, this should be recalculated to the cost of a **Band 7 clinical scientist or a medically qualified Consultant cytopathologist.** There is also another flaw in the costings as to undertake in-clinic reporting	Thank you for your comment. The analysis has been amended to include the role of a cytopathologist. A recent RCPath survey on cytopathology practice in the UK found a 50% split between BMS and pathologists among those performing ROSA. The calculation has been amended accordingly finding a cost of ROSA equal to £70, which is in line with other UK estimates.

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				requires in most situations a biomedical scientist band 4 to prepare and stain the smears, and also a consultant to interpret the smears. The consultant if he or she is in clinic waiting for a specimen is unable to undertake other useful clinical work while waiting for the patient to be examined, the slides to be prepared and be stained by the biomedical scientist.	
UK Endocrine Pathology Society	Evidence review D	102	019 – 021	Lines 19-21 **Please do not suggest use of 'cytospin and cell block' instead of referring to smears**. Making a cytocentrifuge specimen without examining a direct smear first is not performed in most laboratories because direct smears are needed for diagnosis to readily identify thyroid colloid, which is a benign and clinically re-assuring feature. If the whole specimen is processed for a cytocentrifuge preparation as the draft guideline suggests when is says '*consider using cytospin and cell block in addition to, or instead of smear when processing FNAC samples'* colloid will be lost or is more difficult to see.	Thank you for your comment. The committee agreed there is huge variation in practice across centres in the UK. Some of the large thyroid centres in the UK have discontinued preparation of direct smears and only use liquid based cytology for more than 10 years without any negative impact on diagnosis. Colloid can also be visualised on well prepared liquid based cytology. The latter also offers excellent cell preservation and suitable material for ancillary testing. The committee, therefore, recommends either technique can be used. We have updated the wording in the recommendation, rationale and committee discussion in evidence review D to 'liquid based cytology' in response an earlier comment you made on proprietary trademarks. The committee agreed that 'liquid based cytology' is a generic term that includes 'Cytospin and cell block' and is therefore more appropriate to use in a guideline recommendation.
UK Endocrine	Evidence Review D	General	General	**There is no separate stratification of cystic lesions (Thy1c or Thy2c) in this review.** This is important as	Thank you for your comment.

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Pathology Society				most thyroid cysts on ultrasound are benign lesions. The criteria for Thy1 and Thy2 should therefore separate Thy1c and Thy2c as a Thy1c aspirate from a thyroid cyst indicates that the aspirate is not inadequate but in keeping with a benign cyst. Cystic lesions that are surgically excised are almost always removed because they are either suspicious clinically or on imaging or due to compressive symptoms.	Cystic lesions (Thy1c and Thy2c) are now explicitly distinguished in the recommendations. Thy1c was excluded from the recommendation on ROSE and was moved to a different row of the management table as neither ROSE nor CNB is considered appropriate for cystic lesions. Thy2c, has been spelled out in the table with the Thy2 recommendations. It was kept in the same row as the committee agreed that the current management for Thy2 is appropriate for Thy2c aspirates as well.
UK Endocrine Pathology Society	Evidence review D	General	General	Evidence-based review D examines the rates of the various FNA diagnostic categories; Bethesda I-VI, Thy1-Thy5 etc. in patients that undergo surgery alone. Review D does not assess the rates of malignancy in patients who have not undergone surgical excision. Review D does not show robust evidence of the diagnostic accuracy of thyroid FNA for benign lesions of the thyroid that have not undergone surgery. The recommendation to use cytocentrifuge techniques is based on a relatively small number of publications. The efficacy of the FNA technique in this guideline is being assessed in relation to the diagnosis of potential cancer, not in the assessment of whether or not a given thyroid nodule is benign, as benign nodules do not undergo surgery. In routine day to day practice thyroid FNA is used as a test for both benign disease as well as also for cancer.	Thank you for your comment. The committee agreed that it would be difficult to determine malignancy in people who did not have surgery. Therefore, they agreed that the gold standard to use when assessing evidence for diagnostic accuracy was surgical histopathological findings. They also noted that this is how diagnostic accuracy would be assessed in the evidence. There would be people in these studies with benign tumours who would be reported as false positives. Therefore, while not perfect the committee agreed that the evidence does provide evidence on diagnostic accuracy and the subsequent recommendations are based on the best available evidence. Further detail has been added on

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					this in the quality of the evidence section of the committee discussion in evidence report D.
UK Endocrine Pathology Society	Evidence review F	General	General	**Non RCT evidence should not have been excluded in the evidence review**. The purpose of diagnostic testing of thyroid FNA is for diagnosis of cancer versus a benign lesion in thyroid FNA. By excluding non-RCT evidence and not including non-RCT case/control studies almost all the available literature is excluded. Molecular testing requires the cytologist/pathologist to (i)view and report the FNA with a Thy class and then (ii) additional cellular material is sent for molecular testing (Thyroseq, Afirma etc). The molecular data can be analysed and reported by a laboratory blind to the knowledge of the Thy cytology result but these patients cannot be easily randomised in a trial as it would be very difficult to conduct a trial of molecular testing vs. no molecular testing as all the patients not receiving molecular testing on the first occasion would require a repeat ultrasound guided FNA perhaps 3-4 weeks after the first FNA with the cost and ethical issues of a second FNA or core biopsy procedure undertaken for purely research purposes. That is why there is no RCT evidence in the literature. The guideline also ignores some of the other benefits of molecular testing, eg that if certain mutations are present eg BRAF V600E it implies a 99.9% certainty of	Thank you for your comment. The committee noted that this is an area of interest with considerable potential impact on future practice. The committee agreed that there were few molecular tests available in the UK and that without high quality randomised controlled trials (RCTs) demonstrating their cost-effectiveness they would not recommend them. There weren't any RCTs in the area so the committee have made a research recommendation to address this question. "For people who have had fine-needle aspiration samples, where the FNAC sample was adequate but was not able to differentiate between benign and malignant samples, what is the clinical and cost effectiveness of molecular testing?" Please see Appendix J in Evidence review F for further details. The committee do not think that an RCT would be difficult. The research question focuses on comparing molecular tests to usual care in people with indeterminate results. If these guideline recommendations are implemented then usual care would be compared to repeat sampling with FNAC or core needle biopsy, or diagnostic hemithyroidectomy.

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				the presence of thyroid carcinoma whereas the risk of malignancy of a Thy5 FNA for cancer is in the region of 97-99% This may be helpful if extensive surgery is planned such as lateral neck dissection and pre-operative confirmation of malignancy cannot be achieved via other means, if BRAF V600E result shows a mutation. If an Afirma result is negative, the risk of malignancy for a thyroid lesion is below 5%, hence giving reassurance to the patient that an operation is usually not needed The use of molecular testing of all newly diagnosed thyroid cancers is now routine via the NHS England Genomic Hubs as it is of value in selecting targeted therapies for relapsed iodine refractory thyroid cancer	We will flag the inclusion of diagnostic accuracy data to NICE surveillance team for consideration when the guideline is updated. BRAF testing to distinguish benign lesions would not be considered for this evidence review as it is not part of a diagnostic treatment. The committee do not agree that molecular testing as part of diagnostics, prior to surgery, is routinely used in the UK. The guideline review only assesses molecular testing as a diagnostic technique before any surgery (including diagnostic) is undertaken. They agreed that they may be used as part of the treatment pathway in selected cases where there are metastases outside the neck.
UK Endocrine Pathology Society	Guideline	007	009 - 011	1.2.14 Rephrase as it is uncertain what is meant by a 'period of ROSA'? If it needs to be put in place, would it not have to be on going? Rephrase this so that this recommendation refers only to aspirates that are Thy1 so that it does not include Thy 1c (cystic) aspirates.	Thank you for your comment. The mention of the "period of ROSA" has been removed from the recommendation. The recommendation has also been amended to exclude Thy1 (cystic) aspirates.
UK Endocrine Pathology Society	Guideline	007	014 - 016	1.2.15 Table 1 should be amended to left to corner to read 'Thy1 (inadequate) excluding Thy 1c aspirates' in the recommendations:	Thank you for your comment. The management of Thy1c has been added as an additional row as suggested.

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				-Thy1 – Offer repeat FNA in the first instance and correlation with USS. CNB should be offered only after repeated THY1s (> 2) if high risk by US criteria. This is not an option for indeterminate lesions by either BTA / TIRADS. The cytology should be correlated with USS before considering diagnostic hemithyroidectomy. -Thy1c – this category is not addressed at all -Thy2 and 3a - emphasis is on CNB rather than repeat FNA. Usual practice both in the UK and in most overseas centres would be to suggest FNAC first with CNB as second option. CNB should not be used in the evaluation of low risk lesions or solitary U3 lesions. -Thy3a has no mention of reading the words to see what sort of atypia it is. IN fact, everywhere the categories are used as stand-alone diagnoses; within the Thy3a category there are 4 main subtypes of FNA; scanty atypia (SA), scanty microfollicular (SMF), favour benign (FB), and thyroiditis versus neoplasm (TVN), see van der Horst et al. Cytopathology 2020 https://doi.org/10.1111/cyt.12910 -Thy4 and 5 should be dealt with separately not on the same row, they are different, the risks of malignancy are different and the clinical management is different. -col 1 says "(indeterminate)" for both Thy3a and Thy3f but should be "atypical, neoplasm possible" and "follicular" -there is no recommendation for MDT discussion in the table or in the accompanying text	-Thy1 (excluding Thy1c) – The committee do not agree that FNAC should be repeated in the first instance. Both CNB and FNAC with ROSE were shown to improve accuracy, prevent new Thy1 aspirates. Furthermore, CNB was shown to be cost-effective for repeat sampling. The recommendations have been updated to make this clearer so that both CNB and FNAC with ROSE are the first choice, with FNAC alone being an option if those are unavailable or inappropriate**.** This provides flexibility to the centres that may have only one available. - Thy1c – the committee agree this needs a separate row. They recommend repeating FNAC. If the second FNAC is also Thy 1c and the ultrasound appearances are concerning, diagnostic hemithyroidectomy should be considered. - Thy2 and Thy2c – the committee agree that FNAC should be offered first and have amended the recommendation to reflect this. They do not agree that CNB should not be used for Thy2 and Thy3a. It can be useful as it extracts more material. - Thy3a – The committee agreed that CNB was the preferred approach as this reflected the findings of the economic evaluation and clinical review. They have, however, softened the recommendation to a consider.

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				-There is no mention in this document as to the type of needle to use if repeated THY1s are obtained. Guidance should mention use of 27G needles and use of lignocaine with adrenalin to cause vasospasm and allow good access with institution of ROSA if necessary. Use of thicker gauge needles (usually 23G blue needles) invariably produces haemorrhagic and THY1 aspirates.	This will allow flexibility in the cases CNB is unavailable or inappropriate. - Thy4 and Thy5 are grouped together in this table as the recommendations are the same. The table only covers recommendations related to diagnosis and not further management. The column labels were corrected for Thy3a and Thy3f as suggested. The effectiveness of MDTs was not looked at in the guideline and therefore there are no comments on them. The recommendations are made on the basis of what to do regardless of the involvement of the MDT although the committee assume that MDTs are involved in a lot of decisions about care. The literature review did not look at the effectiveness of different needles or lignocaine with adrenaline in FNAC so the committee could not make a specific recommendation on this matter.
UK Endocrine Pathology Society	Guideline	007	005 - 006	For the reasons given below UKEPS have major concerns about widespread implementation of cytocentrifuge/cytospin techniques for **all** thyroid FNA specimens as the draft guideline suggests and we feel that this wording is inappropriate. Well prepared direct smears (MGG and Papanicolaou) are considered crucial in the interpretation of FNA aspirates by most	Thank you for your comment. The committee do not agree that cytospin or cell blocks should not be used when processing FNA samples. However, they do agree that there was not enough evidence to recommend one method over the other. Therefore, the recommendation has been amended to state. 'Use

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				cytopathologists so we disagree with the wording **'Do not use cytospins or cell blocks instead of direct smears when processing FNA samples' .** We would replace it with **'Well prepared direct smears (both air dried and fixed) are preferred for diagnostic purposes. For FNAC consider using a cytocentrifuge technique with cell block if sufficient cytological material is present after examination of direct smears'** (i)Smears are essential for evaluating colloid which is the most useful indicator of benign pathology in thyroid lesions. This is lost completely or very poorly seen in cytocentrifuge/cytospin preparations and in cell block preparations. In addition to loss of background, architecture is also lost in cytocentrifuge/cytospin preparations and cells are seen in 3 dimensional groups making visualization & interpretation difficult. (ii) Diagnostic criteria for diagnosing lesions on FNA are based on a 2 dimensional artefact created by the smearing process used in the making of direct smears. Universal use of cytocentrifuge/cytospin techniques can increase the indeterminate FNA rate by removing background & architectural details, concentrating & compressing cells and tissue fragments into a smaller area and also making interpretation difficult.	liquid based cytology, direct smear or both when processing FNAC samples.' The wording in the recommendation has been updated to 'liquid based cytology' in response to your comment in the last paragraph on proprietary trademarks. The committee agreed that 'liquid based cytology' is a generic term that includes 'Cytospin and cell block' and is therefore more appropriate to use in a guideline recommendation. (i) the committee agreed that colloid can also be visualised on well prepared liquid based cytology. (ii) the committee agreed that architectural details are better seen on a direct smear, however, liquid based cytology offers excellent cell preservation and suitable material for ancillary testing such as immunohistochemistry and molecular testing. (iii & iv & vi) The committee recognise that different centres handle this differently. A review on how to process the specimen was not included as part of the guideline and that level of detail is not included as part of the guideline. (v) the recommendations for ROSA are based on the clinical and cost effectiveness evidence we identified. A threshold analysis identified our cost comparison

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				(iii) Patients would be better served if the guideline emphasized that **'Good quality fixed and air dried direct smears should be prepared at source for Papanicolaou and MGG staining respectively'**. Provision of good quality cytologic material is the cornerstone of diagnostic practice and would not only reduce the inadequate rate but also the indeterminate rate. Overall diagnostic accuracy and reproducibility would be ensured if compliance with this particular factor can be ensured rather than trying to use cytocentrifuge/cytospin and CNB as an aid to compensate for the lack of good quality smears. It should be emphasized that this well known within the pathology community but it is often not understood by other clinicians and aspirators. (iv)Both stains PAP and Romanowsky are essential in making a diagnosis of thyroid lesions especially thyroid cancer and distinguishing between types of thyroid cancer. Both provide complementary information to each other - nuclear morphology is best evaluated on the PAP stain and cytoplasmic detail and background are better seen on the MGG stain. Colloid is not seen well in haemorrhagic aspirates on MGG stain but is visualized very well on fixed PAP stained direct smears - something that cannot be reproduced in cytocentrifuge/cytospin preparations.	analysis would be relatively similar threshold identified by the Royal College of Pathologists (>15%) when Thy1c is excluded. Therefore the committee agreed to use a threshold of >15% in the recommendation.

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				(v) Centres in the UK such as Guy's and St Thomas's in London which have implemented good quality direct smears (MGG and Papanicolaou) with biomedical scientist or pathologist ROSA have consistently been able to achieve Thy1 rates well below 10% with high diagnostic accuracy rates without the need to make use of cytocentrifuge/cytospin techniques, or cell blocks or CNB, (personal communication Dr M Moonim and Dr A Chandra). (vi) Cell blocks are not useful in the diagnosis of benign follicular lesions as there is overlap in the morphologic spectrum of non-neoplastic & neoplastic follicular lesions. The same applies to core needle biopsy including the further disadvantage that CNB may create histopathological artefacts which can simulate malignancy in follicular lesions – an issue which needs to be emphasized. The forthcoming 2022 RCPath Thyroid Cancer Dataset and the British Thyroid Association Thyroid Nodule guidelines currently in preparation advise against using core needle biopsies except in very selected situations, eg after (>=2) repeat Thy1 FNA and for a few other selected indications. '**Cytospin' is a proprietary trademark and it is only one of a number of methods to make cytocentrifuge preparations**. The document refers to fine needle aspiration cytology (FNAC) and	

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				cytocentrifuge techniques which may include cytospin TM. *'Cytospin'* is a UK trademark owned by Thermo Shandon Ltd, Astmoor, Runcorn, Cheshire, WA7 1PR and it is also registered at the US Trademark Office number 3003724 to Thermo Electron Corporation Delaware, 47770 Westinghouse Drive, Fremont, California, 94539, USA and in other jurisdictions also. **Hence throughout the document the word '*cytospin*' if it is to be used it should be replaced by the phrase '*cytocentrifuge technique'*** as there are a number of other methods to make thyroid FNA cyto-centrifuge preparations that are equally effective and which do not require the use of Thermo Shandon laboratory equipment. The fact that the term '*cytospin*' is used in multiple peer reviewed publications without making it clear that it is a proprietary trademark is an oversight in the peer reviewed publications	
UK Endocrine Pathology Society	Guideline	007	005 - 006	**There is no discussion in the guideline or review of the evidence of liquid based cytology (LBC) specimens for diagnosis of cancer by thyroid FNA. This is a significant omission.** The UKEPS would also like to clarify (v) Is the term 'cytospin' referring also to liquid based cytology specimens (LBC)? If not that is an omission, if it is intended to also refer to LBC specimens the wording should be amended.	Thank you for your comment. The wording in the recommendation has been updated to 'liquid based cytology' in response to your comment on proprietary trademarks in the last paragraph. In response to your points: (i) The committee agreed that 'liquid based cytology' is a generic term that includes 'Cytospin and cell block'

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				(vi) What is the meaning the term 'smear' in this guideline? Does 'smear' mean just directly made FNAC smears or does it include liquid based cytology preparations? (vii) Does the guideline need to refer to the specific stains to be used? eg May Grunewald-Giemsa and Papanicolaou or if not at least reference a document that describes the relevant stains, eg The Royal College of Pathologists Guidance on the Reporting of Thyroid Cytology specimens? (viii) **T**he interpretation of LBC techniques is slightly different to direct smears. In LBC specimens the cells shrink slightly due to fixation effects, and thyroid colloid is more difficult to see compared to conventional direct smears stained with Papanicolaou or Giemsa. The omission of any discussion LBC techniques in this guideline is a major oversight and it ought to be corrected**.** Liquid-based cytology (LBC) is claimed to have a diagnostic sensitivity as accurate as conventional smear preparations with excellent cell preservation and the lack of background material on LBC can decrease the number of inadequate diagnoses. The	and is therefore more appropriate to use in a guideline recommendation. (ii) & (iv) The word 'smear' has been updated to 'direct smear' to reflect that it means directly made FNAC smears and not liquid based cytology. (iii) The review protocols didn't include the types of direct smears and therefore the committee has avoided making reference to specific stains used in the guideline. The recommendation has been updated to 'Offer liquid based cytology, direct smear or both when processing FNAC samples.' These changes have been made to the recommendations, rationale and committee discussion of evidence report D.

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				cellular material stored in preservative solution can also be used for the application of immunocytochemical and molecular techniques. The cytologic features are similar to conventional smears but thyroid colloid, lymphocytes and nuclear detail are more easily evaluated in direct smears whereas nuclear details only are better evaluated in LBC slides. Rossi et al. Front. Endocrinol., 16 May 2012 | https://doi.org/10.3389/fendo.2012.00057	
UK Endocrine Pathology Society	Guideline	007	005 - 006	The guideline states, 'consider using cytospin and cell block in addition to, or instead of smear when processing FNAC samples.' This statement is based on an extensive review of the literature in Evidence Review D. This statement could be more appropriately modified to '**Well prepared direct smears (both air dried and fixed) are preferred for diagnostic purposes. For FNAC consider using a cytocentrifuge technique with cell block if sufficient cytological material is present after examination of direct smears'**	Thank you for your comment. The committee do not agree well prepared direct smears are preferred over cytospin or cell blocks. However, they do agree that there was not enough evidence to recommend one method over the other. Therefore, the recommendation has been amended to state. 'Offer liquid based cytology, direct smear or both when processing FNAC samples.' The wording in the recommendation has been updated to 'liquid based cytology' in response to one of your other comments that 'Cytospin' is a proprietary trademark and there is now reference to liquid based cytology in the recommendations. The committee agreed that 'liquid based cytology' is a generic term that includes 'Cytospin and cell block' and is therefore

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					more appropriate to use in a guideline recommendation.
UK Endocrine Pathology Society	Guideline	007	014 - 015	1.2.15 **THY2 (benign). The society disagrees with the conclusion of the draft guideline about the recommendation for the use of CNB for reassessment of lesions with THY2 cytology.** (i) The management option should be reassessed and rephrased. The specificity of a THY2 diagnosis on cytology is >97% while the specificity of a U5 is <60% and that of a U4 less than this. Therefore cytology is superior US and the management should be amended as they are currently incorrect. If a lesion is Thy2 and US low risk there is no value to repeating the FNA or performing CNB. (ii) U3 lesions either solitary or particularly in the context of multinodularity do not require repeat FNA if a THY2 diagnosis is achieved. Discharge to GP or US surveillance if patient is anxious or surgery if the patient is symptomatic would be appropriate options. **(iii)** The recommendation for U4/U5 lesions with THY2 cytology should be to first review US in the MDT and only if high risk should a repeat FNA be offered. CNB should not be utilized as a first option here.	Thank you for your comment. The committee agree that CNB shouldn't be the first choice for repeat sampling in Thy2. However, they also agree it should have less emphasis in the recommendations. CNB is still mentioned as an alternative to FNAC if there is clinical concern. The recommendation states that FNAC should be repeated only if the US continues to reach the threshold of FNAC. This may usually be U3 – U5 but the committee have not stated this as they do not recommend a particular classification system. People with low-risk nodules on the repeated ultrasound will not be required to repeat FNAC. People with concerning US findings may still be required to repeat FNAC but CNB is no longer recommended as a first option. The committee agreed this is in keeping with current practice. The recommendations are consider recommendations to reflect the uncertainty in the evidence base.

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
UK Endocrine Pathology Society	Guideline	007	014 - 015	1.2.15 **Management option, sentence 3 needs rephrasing. CNB should not be utilized as first option here.** This should read ' Discharge people if their FNA results are benign ….'.	Thank you for your comment. The recommendation has been amended to consider FNAC first if the second ultrasound continues to reach the threshold for FNAC. CNB can be considered as an alternative to FNAC. Discharge is recommended for people with a benign FNAC once the benign status is confirmed. the committee recommend considering a repeat FNAC only if the second ultrasound reading is concerning.
UK Endocrine Pathology Society	Guideline	007, 028, 029, 030	General	1.2.15 Various lines **The recommendation to use core biopsy CNB if the 1st FNA is Thy1 or Thy3a is problematic**. (i)Thyroid needle core biopsy is a more complex and risky procedure than FNA, with a higher rate of complications. The UKEPS agrees that CNB has a role in managing repeat assessment of thyroid nodules if multiple FNA (at least 2) are Thy1 provided also that the lesion is high risk on US. (ii) UKEPS would prefer that the FNA is repeated after the first inadequate (with all the guidance on type of needle etc. mentioned above put in place) rather than proceeding directly to CNB in the event of Thy1 or Thy3a.	Thank you for your comment. (i) CNB is more complex and expensive than FNAC. This was explicitly considered both in the health economic analysis, where CNB had a higher procedural cost, and in the recommendations where FNAC is recommended in all cases where CNB seems inappropriate (for instance when the nodule is close to a blood vessel). The committee agreed that CNB is in general considered a more risky procedure than an FNA, but safe in hands of experienced radiologists who are happy to do the procedure except when it is inappropriate. (ii) After a Thy1, both CNB and FNAC with Rapid On-Site Evaluation (ROSE)/Rapid On-Site Assessment (ROSA) were found to be effective in reducing the possibility of receiving an additional Thy1. The

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

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Stakeholder	Document	Page No	Line No	Comments	Developer's response
				(iii) CNB does not help in the diagnosis of follicular lesions (>90% of all thyroid nodules sampled). CNB is unable to discriminate between a benign vs. malignant follicular lesion (iv)CNB produces artefacts which simulate malignancy in follicular lesions on histological assessment of subsequent resections. The recommendation for use of CNB risks leading to many additional cases of thyroid lesions which will be diagnosed as minimally invasive follicular carcinoma due to biopsy artefacts as pathologists are unable to reliably discriminate between what is an artefactual capsular invasion caused by a CNB and what is genuine capsular invasion on subsequent resections. This will be reflected in forthcoming guidance from both the British Thyroid Association and the Royal College of Pathologists where very selected indications for thyroid core biopsy are specified (to be published shortly). (v)This guideline has not taken into consideration in the evidence based review the reduction in THY1 rates and improved diagnostic accuracy (reduction of THY3A rate) seen in centres where 27G needles are used for Thyroid FNA and where lignocaine with adrenalin is used for vasospasm and better needle access in thyroid nodules with significant peripheral vascularity.	committee agreed that these would be expected to reduce repeat Thy1 and therefore the need of diagnostic surgeries. The recommendations have been updated to make this clearer so that both CNB and FNAC with ROSE are the first choice, with FNAC alone being an option if those are unavailable or inappropriate. CNB was also found to be more cost-effective than FNAC after Thy3a, and a consider recommendation was made to allow for alternative options if CNB is not appropriate. The committee agreed that where follicular lesions are suspected this would be categorised as Thy3f and not Thy3a. (iii) The committee agree that neither CNB nor FNAC is helpful in the diagnosis of the follicular lesions. The recommendation for suspected follicular lesions (Thy3f) does not mention any form of repeat biopsy recommending, instead, diagnostic hemithyroidectomy as the only way to discern benign and malignant follicular lesions. (iv) The issue of artefacts left by CNB or FNAC is well known by the committee. Expert members of the committee agreed that CNB can, in some cases, leave "larger" artefacts due to the larger size of the needle, but in their clinical experience never had any issues when discriminating real lesions from artifacts. This

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

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Stakeholder	Document	Page No	Line No	Comments	Developer's response
				(vi)The guideline has not taken into consideration in the evidence-based review the scenario that if ROSA is widely implemented for centres with higher (>15% Thy1 rates excluding Thy1c aspirates) **repeat FNA can be performed in the in-clinic setting so that often a Thy1 can be most often resolved to other Thy categories without a need for CNB.** (vii) The guideline in the evidence base review also takes no account of the fact that most of the published data on thyroid needle core biopsy of the thyroid is from Korea. The incidence and practice of thyroid nodule assessment in Korea is significantly different to that in Europe, North America, and in the UK. Korea practices thyroid screening ultrasound and the incidence and prevalence of thyroid cancer, specifically papillary thyroid cancer in Korea from publications is higher than in the UK based on published evidence. The 'epidemic' of thyroid cancer in South Korea is attributed to US screening, see Park S at al. Association between screening and the thyroid cancer "epidemic" in South Korea: evidence from a nationwide study https://doi.org/10.1136/bmj.i5745**.** and Ahn et al NEJM 2015;373:24:2389-2390 **(viii)There is also evidence that the results achieved for thyroid FNAC are different between centres in Asia, and those in the Europe, North America and the UK** as showing in a recent meta-	further discussion was added to the committee discussion section of evidence report E. The committee did not agree that this issue would make the use of CNB inappropriate in England. (v) The evidence review protocol did not compare FNAC done with different kind of needles and therefore we have not made recommendations in this area. (vi) Both CNB and FNAC with ROSE were shown to improve accuracy and prevent new Thy1 aspirates. Furthermore, CNB was shown to be cost-effective for repeat sampling in the health economic analysis. The recommendations have been updated to make this clearer so that both CNB and FNAC with ROSE are the first choice, with FNAC alone being an option if those are unavailable or inappropriate**.** This provides flexibility to the centres that may have only one available. ROSE is not helpful after Thy3a, so its use is not recommended after that cytology. A separate category has also been added for Thy1c where the committee agreed that FNAC should be repeated, and if the second FNAC is also Thy 1c and the initial ultrasound appearances are concerning then diagnostic hemithyroidectomy should be considered.

				analysis by Vuong et al '*Differences in surgical resection rate and risk of malignancy in thyroid cytopathology practice between Western and Asian countries: A systematic review and meta-analysis'*. Cancer Cytopathology 2020;128:238-249. Compared with Asian practice, western series had a significantly lower risk of malignancy in most of Bethesda categories, whereas the resection rate was not statistically different. Focusing on indeterminate nodules, the resection rate in Western series was significantly higher (51.3% vs 37.6%; P = .048), whereas the risk of malignancy was significantly lower (25.4% vs 41.9%; P = .002) compared with those in Asian series.. This implies that the UK cannot rely on Korean data without looking at first our own experience. In the UK there is only one centre that has published a significant series of patients managed by CNB (the same centre also uses FNA for some but not all patients). This centre showed a Thy1 rate of 45.3% and of 551 patients operated, 149 (27%) were Thy1 and 39 (7%) were Thy1c. See Appukutty SJ. et al J Clin Pathol 2021;0:1-7. In the same centre 7.2% of the core biopsies were inadequate (T1) and 59.3% were indeterminate (T3). 16.5% of the core biopsies were performed after a previous FNA, while 83.5% were performed as the initial diagnostic procedure. **Therefore, it can be inferred that the inadequate rate of CNB (T1) in the UK is not very different to**	(vii) The committee do not agree that most of the evidence on CNB is from South Korea. The meta-analysis (Pyo 2016) that was used to assess accuracy of CNB and FNAC as repeat test after a Thy1 or a Thy3a aspirate includes 26 studies. Of these, only half were conducted in South Korea with the remaining half being European or US studies. Although South Korea may differ in practice and incidence, this is not expected to affect or invalidate studies looking at the accuracy of repeat tests done in people with a previous Thy1 or Thy3a aspirate. (viii) The committee agree that there are differences between western and Asian countries such as those reported in Vuong. This is why the risk of malignancy in all RCPath categories included in the model was informed from a UK meta-analysis (Poller 2020). Hence, the economic analysis is not overestimating prevalence of cancer in the UK. A potentially higher prevalence of cancer in Thy1 and Thy3a aspirates in the Korean studies included in the meta-analysis is not expected to affect or invalidate the accuracy of repeat FNAC or CNB estimated by the meta-analysis. The recommendation for Thy1 has been updated to offer repeat sampling CNB or FNAC with ROSE as the first choice. (ix) The Cambridge Group Study confirms that both FNAC and CNB are suitable initial tests for the evaluation of thyroid nodules. The study did not attempt to compare the usefulness of repeat FNAC vs

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

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Stakeholder	Document	Page No	Line No	Comments	Developer's response
				the expected rate of Thy1 (8.5%) if FNAC is performed with ROSA (Poller DN et al Cytopathology;2020:31(6)502-508) and it does not indicate that CNB is superior to FNA in its diagnostic accuracy. (ix)The subclassification systems for core biopsy used by Korean pathologists for reporting needle core biopsies are also not directly applicable to the UK. The Cambridge group (Appukutty SJ. et al J Clin Pathol 2021;0:1-7) reported 305 of 514 cases as T3 (follicular lesion with architectural or cytological atypia) equivalent to Thy3a/Thy3f. **The society therefore does not support the conclusions of the draft guideline that CNB is superior to or should be used in preference to repeat FNAC for Thy1 lesions than are not Thy 1c** **We also disagree with the draft guideline conclusion that CNB will improve NHS efficiency and reduce overall costs. It is likely that widespread use of** CNB will actually increase NHS costs as: 1.core bx is inconclusive in all follicular lesions (>90% of all thyroid lesions) 2.Widespread use of CNB will likely increase the number of surgeries due to more inconclusive CNB results	CNB after a Thy1 and Thy3a, so it cannot be used to infer whether one is more useful than the other as a second-line test. The committee agree that CNB is more expensive and technically complex and should be used where it is most useful: after a Thy1 (excluding Thy1c) or Thy3a aspirate. These recommendations are supported by the health economic and clinical evidence. However, the committee were aware that there is heterogeneity in practice with some centres preferring FNAC with ROSE so the recommendation was made to include FNAC with ROSE as a valid alternative to CNB for the management of people with Thy1. The committee disagree with the conclusion of this comment. They agreed that: 1. CNB is not recommended after suspected follicular lesions (Thy3f) so there will not be an increase in inconclusive aspirates in follicular lesions 2. CNB has been demonstrated to produce fewer inconclusive results compared to repeat FNAC, so it is expected to reduce the number of surgeries 3. Despite being more expensive than FNAC, the economic model found benefits of CNB to offset its initial cost therefore demonstrating it is cost effective. 4 Artefacts caused by CNB or FNAC are expected to cause minimal impacts as expert members of the

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

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Stakeholder	Document	Page No	Line No	Comments	Developer's response
				3. The cost of the core biopsy in these patients in addition to cost of subsequent diagnostic / therapeutic surgery 4. There will be a cost of managing the additional of cases that may be diagnosed as minimally invasive follicular thyroid carcinoma due to the problems of assessment of CNB and capsular invasion	committee confirmed that a trained histopathologist can distinguish a malignant lesion from an artefact.
UK Endocrine Pathology Society	Guideline	019	001	Table 3 Typo in description of THY3A and F: it should be neoplasm rather than neoplasms.	Thank you for your comment. We have corrected the typos.
UK Endocrine Pathology Society	Guideline	027	006 - 008	The evidence review showing value of FNA with cytocentrifuge/cytopsin and cell block showing high sensitivity (0.937) and specificity (0.825) for identification of nodules as Bethesda Class 3 or above is based on a very small number of published articles (5 studies only). There is a real risk of bias in this conclusion given that this recommendation is only based on 5 studies albeit 1000 plus patients. It is standard practice in **almost all centres if a thyroid nodule is cystic to make a cell block from the FNA material with a direct smear or a cytocentrifuge/cytospin from the cyst content**s but frequently is not mentioned in the methodology in published articles as this is assumed to be normal good clinical practice.	Thank you for your comment. The committee agree that there was not enough evidence to recommend one method over the other. Therefore, have amended the recommendation to state. 'Offer liquid based cytology, direct smear or both when processing FNAC samples.' We have updated the wording in the recommendation to 'liquid based cytology' in response to one of your other comments on proprietary trademarks. The committee agreed that 'liquid based cytology' is a generic term that includes 'Cytospin and cell block' and is therefore more appropriate to use in a guideline recommendation.

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
UK Endocrine Pathology Society	Guideline	027	007	1.2.14 Please state that Thy1c.aspirates should be excluded	Thank you for your comment. The recommendation has been amended to exclude Thy1c (cystic) aspirates.
UK Endocrine Pathology Society	Guideline	027	020 - 021	There is no requirement for cytospin and cell block if smears are properly made and stained. Many major centres do not use a cytospin technique and rely just on smears with a cell block if necessary with excellent diagnostic results.	Thank you for your comment. The evidence favoured cytospin and cell block however, committee agree that this was not enough to recommend one method over the other. Therefore, the recommendation has been amended to state. 'Offer liquid based cytology, direct smear or both when processing FNAC samples.' the wording in the recommendation has been updated to 'liquid based cytology' in response to one of your other comments on proprietary trademarks. The committee agreed that 'liquid based cytology' is a generic term that includes 'Cytospin and cell block' and is therefore more appropriate to use in a guideline recommendation.
UK Endocrine Pathology Society	Guideline	028	021 - 031	The recommendation here to resample THY2 nodules is at variance with most other guidelines as we moved away from resampling THY2 nodules several years back. Since then, in routine practice the incidence of false negative THY2 is exceptionally rare.	Thank you for your comment. The committee's consensus was that the recommendations are similar to some current guidelines, and it would be a change in current practice without clear evidence of benefit to move away from this.
UK Endocrine Pathology Society	Guideline	029	General	The guideline comments that molecular tests are largely unavailable in the NHS and are mostly produced outside the UK but the NICE process for evaluation of new diagnostic tests is to undertake a NICE diagnostic technology appraisal. Why was this not suggested in the draft guideline? It is also possible	Thank you for your comment. The scope of this guideline did not include doing a diagnostic technology appraisal as this follows a different process. We have made research recommendations for molecular testing in the hope that more evidence will be available in the future for any guideline update.

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				to assess the usefulness of a diagnostic test without using RCT evidence	
UK Endocrine Pathology Society	Guideline	029	008 - 009	It begs the question as to how repeat sampling is less useful in THY3F, considering that the most common histological outcome for a THY3F nodule is multinodular goitre/ benign follicular lesion. In patients with multinodular disease, THY3F cytology is a false positive diagnosis in most patients and largely reflects the way a FNA has been performed (operator dependant) or a characteristic in the growth pattern of a goitrous / adenomatoid nodule.	Thank you for your comment. The committee agreed that for suspected follicular lesion (Thy3f), repeat sampling with FNAC or CNB is less useful as they are unable to discriminate between benign and malignant follicular lesion. Hence, the committee agreed that diagnostic hemithyroidectomy is justified in this category, taking into account their high risk of malignancy (around 30%). There were also concerns that, if not followed up with surgery, final diagnosis after Thy3f could take longer to happen. This would delay treatment for a potentially malignant tumour, create uncertainty for the person, and in some centres lead to a longer delay than is allowed by NHS cancer targets. The recommendation is a 'consider' recommendation because the committee agreed is uncertainty in the evidence. Molecular testing may be an option for the future in Thy3f disease however currently there wasn't

Thyroid cancer: assessment and management

Consultation on draft guideline - Stakeholder comments table
23/06/2022 to 04/08/2022

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Stakeholder	Document	Page No	Line No	Comments	Developer's response
					the evidence to recommend it and a research recommendation was made. The committee have relabelled Thy3f from 'indeterminate' to 'suggesting follicular neoplasm' to reflect the Royal College of Pathologists terminology. The committee have updated the rationale to reflect this uncertainty and further detail can be found in the committee discussions of Evidence report E and D and the research protocol for molecular testing is in evidence report E.
UK Endocrine Pathology Society	Guideline	029	026 - 027	The language has changed - ' if there are clinical concerns' This wording needs to be reflected in table 1 where phrasing is very unclear.	Thank you for your comment. We have updated this sentence to state 'The recommendation to consider repeat ultrasound and repeat FNAC with Thy2 reflects current practice and it is not expected to have an impact on NHS resources.'

**None of the stakeholders who comments on this clinical guideline have declared any links to the tobacco industry.*